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In accordance with the Patents (Companies Re-registration) Rules 1982, if a company named in this certificate and any accompanying documents has re-registered under the Companies Act 1980 with the same name as that with which it was registered immediately before re-registration save for the substitution as, or inclusion as, the last part of the name of the words "public limited company" or their equivalents in Welsh, references to the name of the company in this certificate and any accompanying documents shall be treated as references to the name with which it is so re-registered.

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Signed P. Mahoney

Dated 6 June 2003

[redacted]ents Form 1/77

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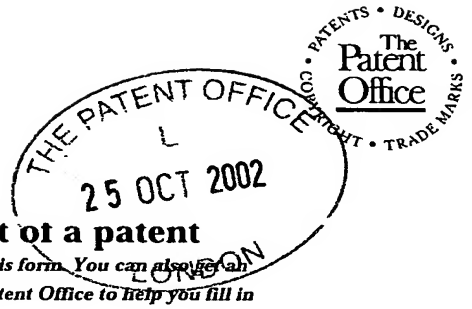

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P01/7700 0.00-0224919.1

Request for grant of a patent

(See the notes on the back of this form. You can also get an explanatory leaflet from the Patent Office to help you fill in this form)

The Patent Office

Cardiff Road
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South Wales
NP10 8QQ

1. Your reference — PC25114

2. Patent application number *(The Patent Office will fill in this part)* — 0224919.1 — 25 OCT 2002

3. Full name, address and postcode of the or of each applicant *(underline all surnames)*

PFIZER LIMITED
Ramsgate Road,
Sandwich,
Kent, CT13 9NJ

Patents ADP number *(if you know it)* 6892673001

If the applicant is a corporate body, give the country/state of its incorporation — United Kingdom

4. Title of the invention — TRIAZOLE COMPOUNDS USEFUL IN THERAPY

5. Name of your agent *(if you have one)*

Dr. S.M. Cosway

"Address for service" in the United Kingdom to which all correspondence should be sent *(including the postcode)*

UK Patent Department
Ramsgate Road,
Sandwich, Kent,
CT13 9NJ
United Kingdom

Patents ADP number *(if you know it)* 1271001

6. If you are declaring priority from one or more earlier patent applications, give the country and the date of filing of the or of each of these earlier applications and *(if you know it)* the or each application number

Country	Priority application number *(if you know it)*	Date of filing *(day / month / year)*

7. If this application is divided or otherwise derived from an earlier UK application, give the number and the filing date of the earlier application

Number of earlier application	Date of filing *(day / month / year)*

8. Is a statement of inventorship and of right to grant of a patent required in support of this request? *(Answer 'Yes' if:*

a) any applicant named in part 3 is not an inventor, or
b) there is an inventor who is not named as an applicant, or
c) any named applicant is a corporate body.
See note (d))

Patents Form 1/77

9. Enter the number of sheets for any of the following items you are filing with this form. Do not count copies of the same document

Continuation sheets of this form	
Description	58
Claim *(s)*	7
Abstract	3
Drawing *(s)*	

10. If you are also filing any of the following, state how many against each item.

Priority documents	
Translations of priority documents	
Statement of inventorship and right to grant of a patent *(Patents Form 7/77)*	
Request for preliminary examination and search *(Patents Form 9/77)*	
Request for substantive examination *(Patents Form 10/77)*	
Any other documents *(please specify)*	

11. I/We request the grant of a patent on the basis of this application.

Signature S.M. Cosway Date 25 October 2002

12. Name and daytime telephone number of person to contact in the United Kingdom: Dr. S.M. Cosway 01304.643723

Warning

After an application for a patent has been filed, the Comptroller of the Patent Office will consider whether publication or communication of the invention should be prohibited or restricted under Section 22 of the Patents Act 1977. You will be informed if it is necessary to prohibit or restrict your invention in this way. Furthermore, if you live in the United Kingdom, Section 23 of the Patents Act 1977 stops you from applying for a patent abroad without first getting written permission from the Patent Office unless an application has been filed at least 6 weeks beforehand in the United Kingdom for a patent for the same invention and either no direction prohibiting publication or communication has been given, or any such direction has been revoked.

Notes

a) If you need help to fill in this form or you have any questions, please contact the Patent Office on 08459 500505.

b) Write your answers in capital letters using black ink or you may type them.

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d) If you have answered 'Yes' Patents Form 7/77 will need to be filed.

e) Once you have filled in the form you must remember to sign and date it.

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Triazole Compounds Useful in Therapy

This invention relates to novel compounds useful in therapy and to processes for the preparation of, intermediates used in the preparation of, compositions containing and the uses of, such derivatives.

WO 01/87855 discloses triazole derivatives as inhibitors of glycine transporter activity. WO 01/58880 and JP2000-63363 disclose triazole derivatives useful as arginine Vasopressin V_{1A} receptor antagonists. Kakefuda et al., Bioorg. Med. Chem. 10 (2002) 1905-1912 and Kakefuda et al., J.Med.Chem., 2002, 45, 2589-2598 discuss the utility of 4,5-diphenyl-1,2,4-triazole derivatives as selective antagonists for the human V_{1A} receptor and comment that the 4,5-diphenyl-1,2,4-triazole structure plays an essential role in V_{1A} affinity.

The compounds of the present invention have been found to have useful pharmaceutical properties. They may be used to treat aggression, Alzheimer's disease, anorexia nervosa, anxiety disorder, asthma, atherosclerosis, cardiac failure, cardiovascular disease, cataract, central nervous system disease, cerebrovascular ischemia, cirrhosis, cognitive disorder, Cushing's disease, depression, diabetes mellitus, dysmenorrhoea, edema, emesis, endometriosis, gastrointestinal disease, glaucoma, gynaecological disease, heart disease, hypertension, hyponatremia, ischemia, ischemic heart disease, lung tumor, micturition disorder, motion sickness, neoplasm, nephrotoxicity, non-insulin dependent diabetes, obesity, obsessive/compulsive disorder, ocular hypertension, premature labor, pulmonary disease, Raynaud's disease, renal disease, renal failure, male and female sexual dysfunction, sleep disorder, spinal cord injury, thrombosis, urogenital tract infection, urolithiasis. In particular, they exhibit vasopressin antagonistic activity and can be used in the treatment of dysmenorrhoea.

There is a high unmet need in the area of menstrual disorders and it is estimated that up to 90% of all menstruating women are affected to some degree. Up to 42% of women miss work or other activities due to menstrual pain and it has been estimated that around 600 million work hours a year are lost in the US as a result (costing around $2 billion in lost productivity).

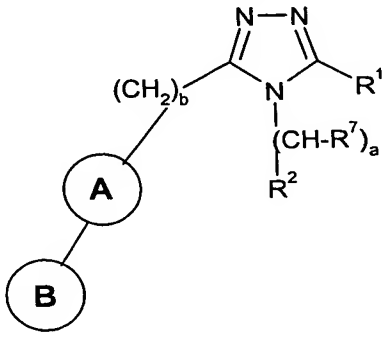
Menstrual pain in the lower abdomen is caused by myometrial hyperactivity and reduced uterine blood flow. These pathophysiological changes result in abdominal pain that radiates out to the back and legs. This may result in women feeling nauseous, having headaches and suffering from insomnia. This condition is called dysmenorrhoea and can be classified as either primary or secondary dysmenorrhoea.

Primary dysmenorrhoea is diagnosed when no abnormality causing the condition is identified. This affects up to 50% of the female population. Where an underlying gynaecological disorder is present, such as endometriosis, pelvic inflammatory disease (PID), fibroids or cancers, secondary dysmenorrhoea will be diagnosed. Secondary dysmenorrhoea is diagnosed in only approximately 25% of women suffering from dysmenorrhoea. Dysmenorrhoea can occur in conjunction with menorrhagia, which accounts for around 12% of referrals to gynaecology outpatients departments.

Currently, women suffering from primary dysmenorrhoea are treated with non-steroidal anti-inflammatory drugs (NSAID's) or the oral contraceptive pill. In cases of secondary dysmenorrhoea surgery may be undertaken to correct the underlying gynaecological disorder.

Women suffering from dysmenorrhoea have circulating vasopressin levels which are greater than those observed in healthy women at the same time of the menstrual cycle. Inhibition of the pharmacological actions of vasopressin, at the uterine vasopressin receptor, may prevent dysmenorrhoea.

According to the present invention there is provided a compound of formula **(I)**,



(I)

or a pharmaceutically acceptable salt or solvate thereof, wherein

R^1 represents C_1-C_6 alkyl, -$(CH_2)_c$-[C_3-C_8 cycloalkyl]-, -$(CH_2)_c$-W or -$(CH_2)_c$-Z-$(CH_2)_d$-W;

R^2 represents a phenyl group, optionally fused to a 5- or 6- membered aryl or heterocyclic group which may contain one or more heteroatoms selected from N, O or S; the phenyl group and the optionally fused group being optionally substituted with one or more groups independently selected from the list defined below;

Ring **A** represents a 4-, 5- or 6- membered saturated heterocyclic group containing at least one N;

Ring **B** represents a phenyl group or het^1, each group being optionally substituted with one or more groups independently selected from the list defined below;

het^1 represents a 4-, 5- or 6- membered saturated, or unsaturated, heterocyclic group containing at least one N (but which may also contain one or more O or S atoms);

R^7 independently represents H, C_1-C_6 alkyl, OR^3, -$(CH_2)_e$-R^3 or -$(CH_2)_f$-O-$(CH_2)_e$-R^3;

W represents a phenyl group, NR^4R^5 or het^2, the phenyl group being optionally substituted with one or more groups independently selected from halogen, CF_3, OCF_3, R^3, OR^3, CO_2R^3, $CONR^4R^5$, CN, $SO_2NR^4R^5$ and NR^3SO_2Me;

het^2 represents a 4-, 5-, 6- or 7- membered saturated, or unsaturated, heterocyclic group containing at least one N (but which may also contain one or more O or S atoms), optionally substituted with one or more groups independently selected from the list defined below;

Z represents O or $S(O)_g$;

g represents 0, 1 or 2;

het^3 represents a 4-, 5-, 6- or 7- membered saturated or unsaturated heterocyclic group containing at least one N (but which may also contain one or more O or S atoms), optionally substituted with one or more groups independently selected from the list defined below;

at each occurrence R^3 and R^6 independently represent H, C_1-C_6 alkyl optionally substituted by Y, -$(CH_2)_g$-[C_3-C_8 cycloalkyl], phenyl, benzyl, pyridyl or pyrimidyl;

Y independently represents a phenyl group, NR^4R^5 or het^3, the phenyl group being optionally substituted with one or more groups independently selected from halogen, CF_3, OCF_3, R^4, OR^4, CO_2R^4, $CONR^4R^5$, CN, $SO_2NR^4R^5$, NR^4SO_2Me and -NR^4R^5;

At each occurrence R^4 and R^5 independently represent H, C_1-C_6 alkyl, -$(CH_2)_g$-[C_3-C_8 cycloalkyl], phenyl, benzyl, pyridyl or pyrimidyl; or R^4 and R^5 together with the N atom to which they are attached represent a heterocyclic group of from 3 to 8 atoms;

Substituents for R^2, Ring **B**, het^1, het^2 and het^3 are independently selected from the following list: halogen, CF_3, OCF_3, R^3, -$(CH_2)_e$-OR^3, -$(CH_2)_e$-CO_2R^3, -$(CH_2)_e$-$CONR^4R^5$, -$(CH_2)_e$-CN, -$(CH_2)_e$-$SO_2NR^4R^5$, -$(CH_2)_e$-NR^3SO_2Me, -$(CH_2)_e$-COR^3, -$(CH_2)_e$-$OCOR^3$, -$(CH_2)_e$-$NHCOR^3$, -$(CH_2)_e$-NR^3COR^6 and -$(CH_2)_e$$NR^4R^5$;

a and b independently represent 0 or 1;

c, d, e and g independently represent 0, 1, 2, 3 or 4;

f independently represents 1, 2, 3 or 4;

provided that a + b cannot equal 0; and

provided that when R^1 represents -$(CH_2)_c$-Z-$(CH_2)_d$-W and W represents NR^4R^5 or any N linked heterocyclic group then d must not be 0 or 1; and

provided that when R^2 represents a phenyl group substituted by a group of formula -$(CH_2)_e$$OR^3$, -$(CH_2)_e$-$CO_2R^3$ or -$(CH_2)_e$$OCOR^3$; or
het^1 and/or het^2 are substituted by a group of formula -$(CH_2)_e$$OR^3$, -$(CH_2)_e$-$CO_2R^3$ or -$(CH_2)_e$$OCOR^3$; or
when R^7 represents -OR^3 or -$(CH_2)_f$-O-$(CH_2)_e$-R^3 and e is 0; or
when W represents a phenyl group substituted with -OR^3 or -CO_2R^3;

and R^3 represents an alkyl group substituted with Y, and Y represents NR^4R^5 or an N-linked het[3];
then R^3 must represent C_2-C_6 alkyl substituted with Y.

One skilled in the art would understand that an amine moiety spaced from another heteroatom by only a methylene link would be unstable upon exposure to hydrolytic media.

In the above definitions, halogen means fluoro, chloro, bromo or iodo. Alkyl, alkyloxy, alkanoyl, alkylene, alkenyl and alkenylene groups containing the requisite number of carbon atoms, except where indicated, can be unbranched or branched chain. Examples of alkyl include methyl, ethyl, n-propyl, i-propyl, n-butyl, i-butyl, sec-butyl and t-butyl. Examples of alkoxy include methoxy, ethoxy, n-propoxy, i-propoxy, n-butoxy, i-butoxy, sec-butoxy and t-butoxy. Examples of alkylene include methylene, 1,1-ethylene, 1,2-ethylene, 1,3-propylene and 1,2-propylene. Examples of cycloalkyl include cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl and cycloheptyl. Examples of cycloalkylene include cyclopropylene, cyclobutylene, cyclopentylene, cyclohexylene and cycloheptylene.

Preferred heterocycles included within the definition of "heterocycle" are pyrrolyl, imidazolyl, triazolyl, thienyl, furyl, thiazolyl, oxazolyl, thiadiazolyl, oxadiazolyl, pyridinyl, pyrimidinyl, pyridazinyl, pyrazinyl, indolyl, isoindolyl, quinolinyl, isoquinolinyl, benzimidazolyl, quinazolinyl, phthalazinyl, benzoxazolyl and quinoxalinyl, together with partially or fully saturated versions thereof as well as azetidinyl, pyrrolidinyl, piperidinyl, piperazinyl, homopiperazinyl and morpholinyl.

Preferred groups of compounds are those in which:

(i) R^1 is C_1-C_4 alkyl and more preferably methyl, i-propyl or n-butyl;

(ii) R^1 is $-(CH_2)_c$-[C_3 cycloalkyl]-;

(iii) R^2 is a phenyl group optionally substituted with one or more groups selected from halogen or $-(CH_2)_e$-OR^3;

(iv) ring **A** is selected from piperidinyl, piperazinyl, azetidinyl or pyrrolidinyl and more preferably it is piperidinyl;

(v) ring **B** is a phenyl group substituted groups one or more groups selected from halogen, CF_3, OCF_3, R^3, $-(CH_2)_e$-OR^3 and CN;

(vi) ring **B** is an unsubstituted phenyl group;

(vii) R^7 is C_1-C_4 alkyl, more preferably it is C_1-C_4 straight chain alkyl and most preferably it is methyl or ethyl;

(viii) R^7 is CH_2OH;

(ix) W is a halo substituted phenyl group;

(x) W is NR^4R^5, preferably it is selected from NHMe, NMe_2, NEt_2, $N(iPr)_2$, or $N(nPr)_2$;

(xi) Z is O;

(xii) R^3 and R^6 are independently C_{1-4} alkyl, more preferably unsubstituted C_{1-4} alkyl;

(xiii) R^4 and R^5 are independently selected from methyl, ethyl, n-propyl or i-propyl;

(xiv) R^4 and R^5 together with the nitrogen to which they are attached form a heterocycle preferably selected from piperidinyl, 2-oxa-5-aza-bicyclo[2.2.1]heptanyl, piperazinyl, azetidinyl, morpholinyl and pyrrolidinyl;

(xv) het^1 is selected from optionally substituted pyridinyl, pyrimidinyl, pyrazinyl, pyridazinyl, triazinyl, triazolyl, tetrazolyl, pyrrolyl, pyrazolyl, imidazolyl, oxazolyl, isoxazolyl, thiazolyl, piperidinyl, piperazinyl, azetidinyl, morpholinyl, 2-oxa-5-aza-bicyclo[2.2.1.]heptanyl or pyrrolidinyl, and more preferably selected from pyridinyl or pyrimidinyl, optionally substituted by any one of R^3;

(xvi) het^2 is selected from substituted or unsubstituted pyridinyl, pyrimidinyl, pyrazinyl, pyridazinyl, triazinyl, triazolyl, tetrazolyl, pyrrolyl, pyrazolyl, imidazolyl, oxazolyl, isoxazolyl, thiazolyl, piperidinyl, piperazinyl, N-methyl piperazinyl, azetidinyl, morpholinyl, 2-oxa-5-aza-bicyclo[2.2.1]heptanyl or pyrrolidinyl and more preferably selected from imidazolyl, piperidinyl, piperazinyl, N-methyl piperazinyl, azetidinyl, morpholinyl, 2-oxa-5-aza-bicyclo[2.2.1]heptanyl or pyrrolidinyl;

(xvi) a is 1;

(xvii) b is 0;

(xviii) c is selected from 0, 1 or 2. More preferably it is selected from 0 or 1;

(xix) e is selected from 0, 1 or 2 and more preferably selected from 0 or 1;

(xxi) d is selected from 0, 1, 2 or 3 and more preferably it is selected from 0 or 2;

(xxiii) f is selected from 1 or 2;

(xxvi) g is 0.

Preferred compounds according to the present invention are:
(*S*)-4-[5-Butyl-4-(1-phenyl-ethyl)-4*H*-[1,2,4]triazol-3-yl]-3,4,5,6-tetrahydro-2*H*-[1,2']bipyridinyl;
2-[4-(4-Benzyl-5-isobutyl-4*H*-[1,2,4]triazol-3-yl)-piperidin-1-yl]-pyrimidine;
(*S*)-4-[5-Methyl-4-(1-phenyl-ethyl)-4*H*-[1,2,4]triazol-3-yl]-3,4,5,6-tetrahydro-2*H*-[1,2']bipyridinyl;
4-[4-Benzyl-5-butyl-4*H*-[1,2,4]triazol-3-yl]-3,4,5,6-tetrahydro-2*H*-[1,2']bipyridinyl;
2-[4-(4-Benzyl-5-isopropyl-4*H*-[1,2,4]triazol-3-yl)-piperidin-1-yl]-pyrimidine;
2-[4-(4-Benzyl-5-cyclopropyl-4*H*-[1,2,4]triazol-3-yl)-piperidin-1-yl]-pyrimidine;
(*S*)-2-{4-[5-Methyl-4-(1-phenyl-propyl)-4*H*-[1,2,4]triazol-3-yl)-piperidin-1-yl]-pyrimidine;
2-[4-(4-Benzyl-5-propyl-4*H*-[1,2,4]triazol-3-yl)-piperidin-1-yl]-pyrimidine;
2-{4-[4-Benzyl-5-(2-chloro-phenoxymethyl)-4*H*-[1,2,4]triazol-3-yl]-piperidin-1-yl}-pyrimidine;
2-[4-(4-Benzyl-5-butyl-4*H*-[1,2,4]triazol-3-yl)-piperidin-1-yl]-pyrimidine;
(*S*)-2-{4-[5-Methyl-4-(1-phenyl-ethyl)-4*H*-[1,2,4]triazol-3-yl)-piperidin-1-yl]-pyrimidine;
2-{4-[4-Benzyl-5-(4-fluoro-phenoxymethyl)-4*H*-[1,2,4]triazol-3-yl]-piperidin-1-yl}-pyrimidine;
2-{4-[5-Methyl-4-(3-methyl-benzyl)-4*H*-[1,2,4]triazol-3-yl)-piperidin-1-yl]-pyrimidine;
(*S*)-2-{4-[5-Methyl-4-(1-phenyl-ethyl)-4*H*-[1,2,4]triazol-3-ylmethyl]-piperidin-1-yl}-pyrimidine;
2-{4-[4-(3-Fluoro-benzyl)-5-methyl-4*H*-[1,2,4]triazol-3-yl)-piperidin-1-yl]-pyrimidine;
4-(4-Benzyl-5-morpholin-4-ylmethyl-4*H*-[1,2,4]triazol-3-yl)-3,4,5,6-tetrahydro-2*H*-[1,2']bipyridinyl;
4-(4-Benzyl-5-benzyloxymethyl-4*H*-[1,2,4]triazol-3-yl)-3,4,5,6-tetrahydro-2*H*-[1,2']bipyridinyl;
4-(4-Benzyl-5-methyl-4*H*-[1,2,4]triazol-3-yl)-3,4,5,6-tetrahydro-2*H*-[1,2']bipyridinyl;
(*R*)-2-[3-Methyl-5-(1-pyrimidin-2-yl-piperidin-4-yl)-[1,2,4]triazol-4-yl]-2-phenyl-ethanol;
2-[4-(4-Benzyl-5-methyl-4*H*-[1,2,4]triazol-3-yl)-piperidin-1-yl]-4-methyl-pyrimidine;
2-[4-(4-Benzyl-5-methyl-4*H*-[1,2,4]triazol-3-yl)-piperidin-1-yl]-pyrimidine;
4-(4-Benzyl-5-methyl-4*H*-[1,2,4]triazol-3-yl)-1-phenyl-piperidine;
2-[4-(4-Benzyl-5-methyl-4*H*-[1,2,4]triazol-3-yl)-piperidin-1-yl]-pyrazine;
4-(4-Benzyl-5-piperidin-1-ylmethyl-4H-[1,2,4]triazol-3-yl)-3,4,5,6-tetrahydro-2H-[1,2']bipyridinyl;
(*S*)-4-[4-(1-Phenyl-ethyl)-5-piperidin-1-ylmethyl-4*H*-[1,2,4]triazol-3-yl]-3,4,5,6-tetrahydro-2*H*-[1,2']bipyridinyl;

4-[4-Benzyl-5-(4-methoxy-piperidin-1-ylmethyl)-4*H*-[1,2,4]triazol-3-yl]-3,4,5,6-tetrahydro-2*H*-[1,2']bipyridinyl;
(*S*)-4-[5-(4-Methoxy-piperidin-1-ylmethyl)-4-(1-phenyl-ethyl)-4*H*-[1,2,4]triazol-3-yl]-3,4,5,6-tetrahydro-2*H*-[1,2']bipyridinyl;
4-[4-Benzyl-5-(3,4,5,6-tetrahydro-2H-[1,2']bipyridinyl-4-yl)-4H-[1,2,4]triazol-3-ylmethyl]-piperazine-1-carboxylic acid benzyl ester;
4-[4-Benzyl-5-(2-morpholin-4-yl-ethoxymethyl)-4H-[1,2,4]triazol-3-yl]-3,4,5,6-tetrahydro-2H-[1,2']bipyridinyl.

The pharmaceutically acceptable salts of the compounds of formula **(I)** include the acid addition and base salts thereof.

Suitable acid addition salts are formed from acids which form non-toxic salts and examples are the hydrochloride, hydrobromide, hydroiodide, sulphate, bisulphate, nitrate, phosphate, hydrogen phosphate, acetate, maleate, fumarate, lactate, tartrate, citrate, gluconate, succinate, accharate, benzoate, methanesulphonate, ethanesulphonate, benzenesulphonate, p-toluenesulphonate, palmoate and pamoate salts.

Suitable base salts are formed from bases, which form non-toxic salts and examples are the sodium, potassium, aluminium, calcium, magnesium, zinc and diethanolamine salts.

For a review on suitable salts see Berge et al, J.Pharm.Sci., 66, 1-19, 1977.

The pharmaceutically acceptable solvates of the compounds of formula **(I)**, or salts thereof include the hydrates thereof.

Also included within the scope of the present invention are the polymorphs of compounds of formula **(I)**.

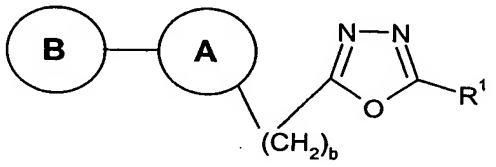
A compound of the formula **(I)** may contain one or more asymmetric carbon atoms and therefore exist in two or more stereoisomeric forms. The present invention also includes the individual stereoisomers of the compounds of the formula **(I)** and, where appropriate, the individual tautomeric forms thereof, together with mixtures thereof.

Separation of diastereoisomers or cis and trans isomers may be achieved by conventional techniques, e.g. by fractional crystallisation, chromatography or H.P.L.C. of a stereoisomeric mixture of a compound of the formula **(I)** or a suitable salt or derivative thereof. An individual enantiomer of a compound of the formula **(I)** may also be prepared from a corresponding optically pure intermediate or by resolution, such as H.P.L.C. of the corresponding racemate using a suitable chiral support or by fractional crystallisation of the diastereoisomeric salts formed by reaction of the corresponding racemate with a suitable optically active acid or base, as appropriate.

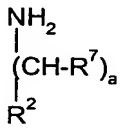
The present invention also includes all suitable isotopic variations of a compound of the formula **(I)**, or a pharmaceutically acceptable salt thereof. An isotopic variation of a compound of the formula **(I)** or a pharmaceutically acceptable salt thereof is defined as one in which at least one atom is replaced by an atom having the same atomic number but an atomic mass different from the atomic mass usually found in nature. Examples of isotopes that can be incorporated into compounds of the formula **(I)** and pharmaceutically acceptable salts thereof include isotopes of hydrogen, carbon, nitrogen, oxygen, phosphorus, sulphur, fluorine and chlorine such as ^{2}H, ^{3}H, ^{13}C, ^{14}C, ^{15}N, ^{17}O, ^{18}O, ^{31}P, ^{32}P, ^{35}S, ^{18}F and ^{36}Cl, respectively. Certain isotopic variations of the compounds of the formula **(I)** and pharmaceutically acceptable salts thereof, for example, those in which a radioactive isotope such as ^{3}H or ^{14}C is incorporated, are useful in drug and/or substrate tissue distribution studies. Tritiated, i.e. ^{3}H, and carbon-14, i.e. ^{14}C, isotopes are particularly preferred for their ease of preparation and detectability. Further, substitution with isotopes such as deuterium, i.e. ^{2}H, may afford certain therapeutic advantages resulting from greater metabolic stability, for example, increased *in vivo* half-life or reduced dosage requirements and hence may be preferred in some circumstances. Isotopic variations of the compounds of formula **(I)** and pharmaceutically acceptable salts thereof, according to this invention, can generally be prepared by conventional procedures such as by the illustrative methods or by the preparations described in the Examples and Preparations hereafter using appropriate isotopic variations of suitable reagents.

According to the present invention there is also provided a process for the production of a compound of formula **(I)**, which comprises:

a) reacting a compound of formula **(II)** with a compound of formula **(III)**



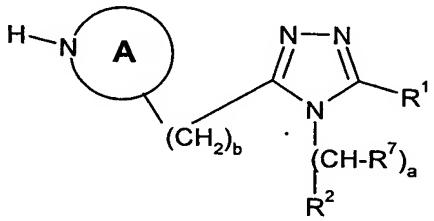
(II)



(III)

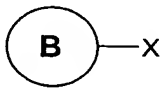
in which ring A and ring B, R^1, R^2, R^{42}, a and b are as hereinbefore defined.

b) reacting a compound of formula **(VI)**



(VI)

in which ring A, R^1, R^2, R^7, a and b are as hereinbefore defined, with a compound of formula **(VII)**



(VII)

in which ring B is as defined above and X represents a leaving group such as halogen.

Unless otherwise provided herein:

WSCDI means 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride;

DCC means N,N'-dicyclohexylcarbodiimide;

HOAT means 1-hydroxy-7-azabenzotriazole;

HOBT means 1-hydroxybenzotriazole hydrate;

PyBOP® means Benzotriazol-1-yloxytris(pyrrolidino)phosphoniumhexa fluorophosphate;

PyBrOP® means bromo-tris-pyrrolidino-phosphoniumhexafluoro phosphate;

Mukaiyama's reagent means 2-chloro-1-methylpyridinium iodide;

KHMDS means potassium bis(trimethylsilyl)amide;

Hünig's base means N-ethyldiisopropylamine;

Et_3N means triethylamine;

NMM means N-methylmorpholine;

HMDS means hexamethyldisilazane

BINAP means 2,2'-bis(diphenylphosphino)-1,1'-binaphthyl;

Dba means dibenzylideneacetone;

Boc means *tert*-butoxycarbonyl;

CBz means benzyloxycarbonyl;

p-TSA means *p*-toluenesulphonic acid

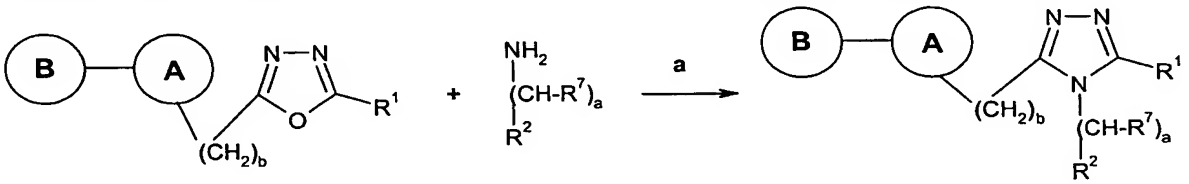
TBAF means tetra-butyl ammonium fluoride

MeOH means methanol, EtOH means ethanol, and EtOAc means ethyl acetate;

THF means tetrahydrofuran, DMSO means dimethyl sulphoxide, and DCM means dichloromethane, DMF means N,N-dimethylformamide, NMP means N-methyl-2-pyrrolidinone;

AcOH means acetic acid, TFA means trifluoroacetic acid.

The following schemes illustrate the preparation of compounds of the formula **(I)**, throughout which Rings A and B, R^1, R^2, R^7, a and b are as hereinbefore defined:



(II) **(III)** **(I)**

Scheme 1.

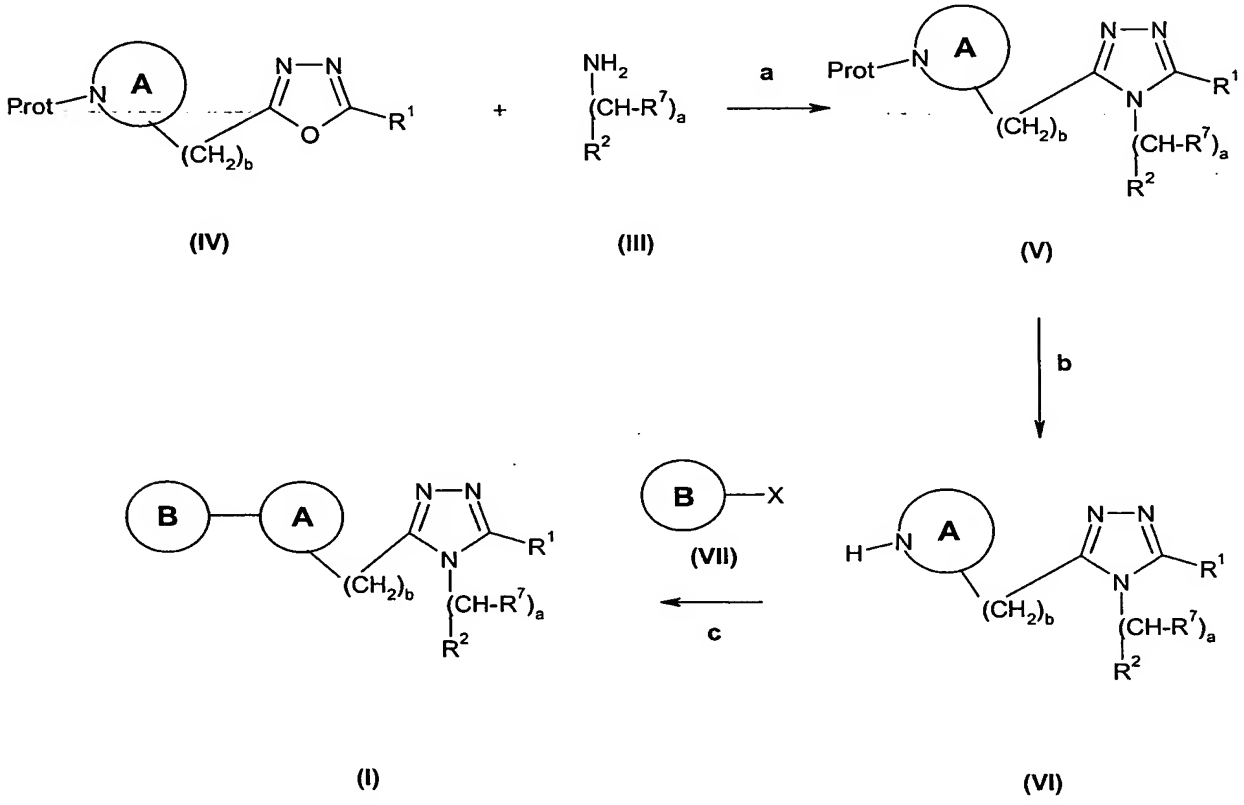
Amines suitable for use as compound **(III)** are commercially available or are known in the literature.

Step (a): Benzylamine **(III)** is reacted with oxadiazole **(II)** to give the compound of formula **(I)**. This reaction is carried out by heating the starting materials to elevated temperatures such as 100-150°C for 1 to 48 hours with a suitable acidic catalyst such as

p-TSA, or Lewis acid catalyst such as magnesium chloride, optionally using a high boiling solvent such as xylene.

Preferred conditions are: 2 eq. of amine **(III)** with 0.4 eq. magnesium chloride at 140°C for 1-18 hours, or 1.2 eq. amine **(III)**, cat. P-TSA, in xylene for 48 hrs.

When ring B is linked to A via an N atom, then:



Scheme 2.

Prot represents a suitable protecting group for nitrogen. Standard methodology for nitrogen protecting groups is used, such as that found in textbooks, (e.g. "Protecting Groups in Organic Synthesis" by T.W. Greene and P. Wutz).

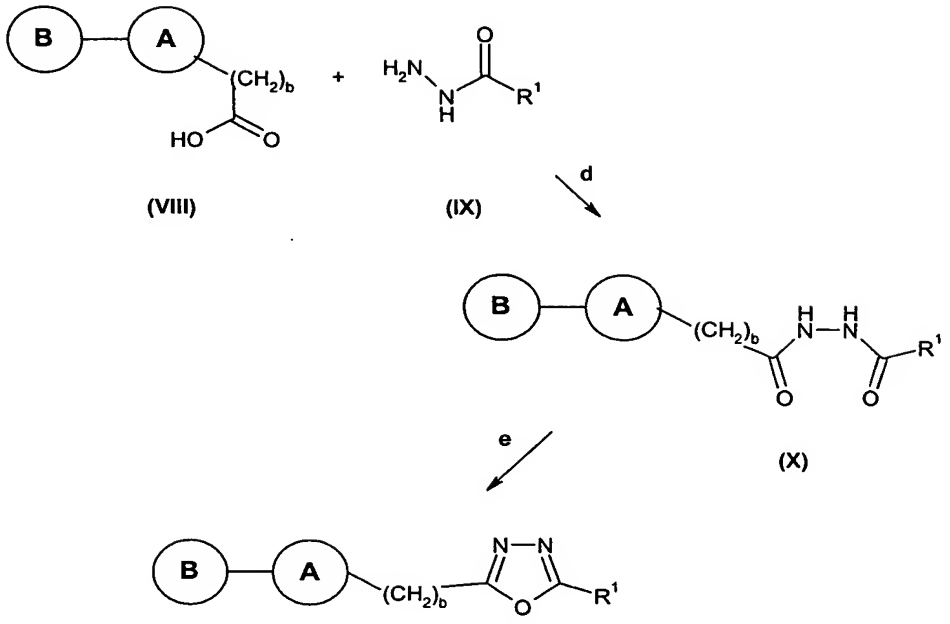
X represents a leaving group such as halogen.

Compounds suitable for use as compound **(VII)** are commercially available or are known in the literature.

Step (b): Deprotection of compound **(V)** is undertaken using standard methodology, as described in "Protecting Groups in Organic Synthesis" by T.W. Greene and P. Wutz".
When Prot is Boc the preferred method is hydrogen chloride in a suitable solvent such as 1,4-dioxane at room temperature for 1-16 hours, or a solution of trifluoroacetic acid in dichloromethane for 1-2 hours.
When Prot is CBz the preferred method is hydrogenolysis using a suitable palladium catalyst in a solvent such as ethanol.
When Prot is an allyl carbamate, preferred conditions are thiobenzoic acid and a suitable palladium catalyst such as $Pd_2(Dba)_3$ with a suitable phosphine additive such as 1,4-bis(diphenylphosphino)butane in tetrahydrofuran for 20 minutes.

Step (c): Arylation of compound **(VI)** can be carried out by a palladium catalysed cross-coupling reaction using a suitable base (*t*-BuONa), a catalytic amount of suitable additive such as 2,2'-bis(diphenylphosphino)-1,1'-binaphthyl and a suitable palladium catalyst in toluene at elevated temp for 1 to 24 hours under an inert atmosphere, to give compound **(I)**. Alternatively compound **(I)** can be prepared by reaction of the amine **(VI)** with compound **(VII)** by heating at elevated temperature such as 50°C -140°C in a suitable solvent such as DMF, NMP or 1,4-dioxan for about 1-48 hrs with a base such as potassium carbonate, sodium hydrogen carbonate or Hünig's base.
Preferred conditions are: 1-2.5 eq. Halide **(VII)** 1-2 eq. potassium carbonate in N,N-dimethylformamide at 50 °C for 4-18 hours, or, 1-2.5 eq. Halide **(VII)**, 2-3 eq. Hünig's base, in 1,4-dioxan or NMP at reflux for 18-48 hrs, or, 1 eq. Halide **(VII)**, 3.5 eq. NaOt-Bu, 0.08eq BINAP, 0.4 eq. $Pd(dba)_2$, in toluene for 8 hrs at 70°C.

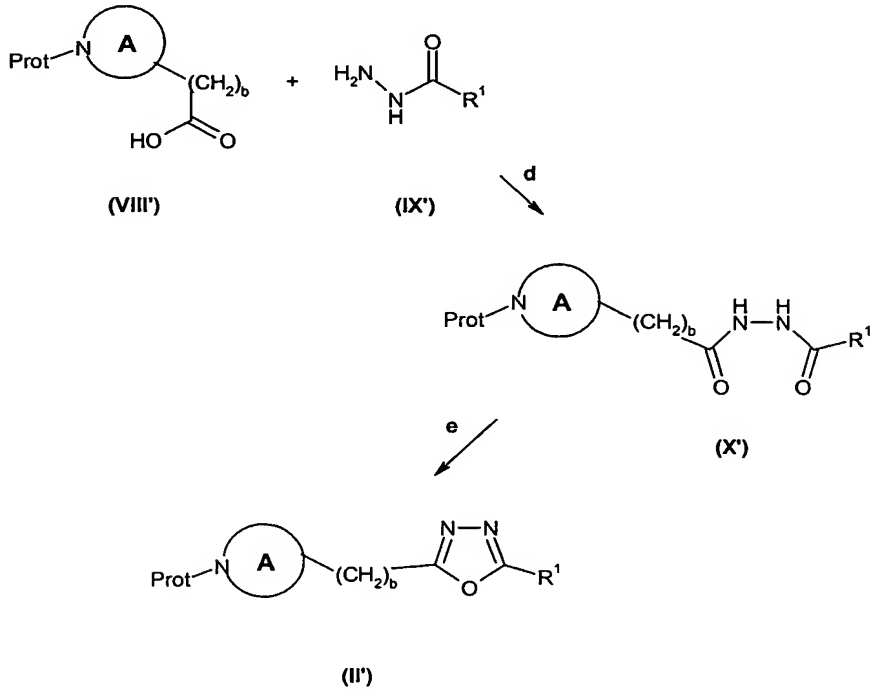
Compounds suitable for use as compounds **(II)** and **(IV)** are known in the literature or can be prepared as shown in scheme 3.1 and 3.2.



(II)

Scheme 3.1

When rings A and B are linked through an N atom then:



(II')

Scheme 3.2

Compounds **(VIII)/(VIII')** and **(IX)** are either commercially available or are known in methodology such as the hydrolysis of the corresponding ester. (see Preparation 1).

Step (d): Reaction of carboxylic acid **(VIII/VIII')** with hydrazide **(IX)** can be carried out by standard methods.

Coupling may be undertaken by using either

(i) an acyl chloride derivative of acid **(VIII/VIII')** + hydrazide **(IX)**, with an excess of acid acceptor in a suitable solvent, or

(ii) the acid **(VIII/VIII')** with a conventional coupling agent + hydrazide **(IX)**, optionally in the presence of a catalyst, with an excess of acid acceptor in a suitable solvent.

Typically the conditions are as follows:

(i) acid chloride of acid **(VIII/VIII')** (generated in-situ), an excess of hydrazide, optionally with an excess of 3° amine such as Et_3N, Hünig's base or NMM, in DCM or THF, without heating for 1 to 24 hrs,

or

(ii) acid **(VIII/VIII')**, WSCDI /DCC and HOBT /HOAT, an excess of hydrazide **(IX)**, with an excess of NMM, Et_3N, Hünig's base in THF, DCM or EtOAc, at rt. for 4 to 48 hrs; or, acid **(VIII/VIII')**, PYBOP®/PyBrOP®/Mukaiyama's reagent, an excess of hydrazide **(IX)**, with an excess of NMM, Et_3N, Hünig's base in THF, DCM or EtOAc, at rt. for 4 to 24 hrs.

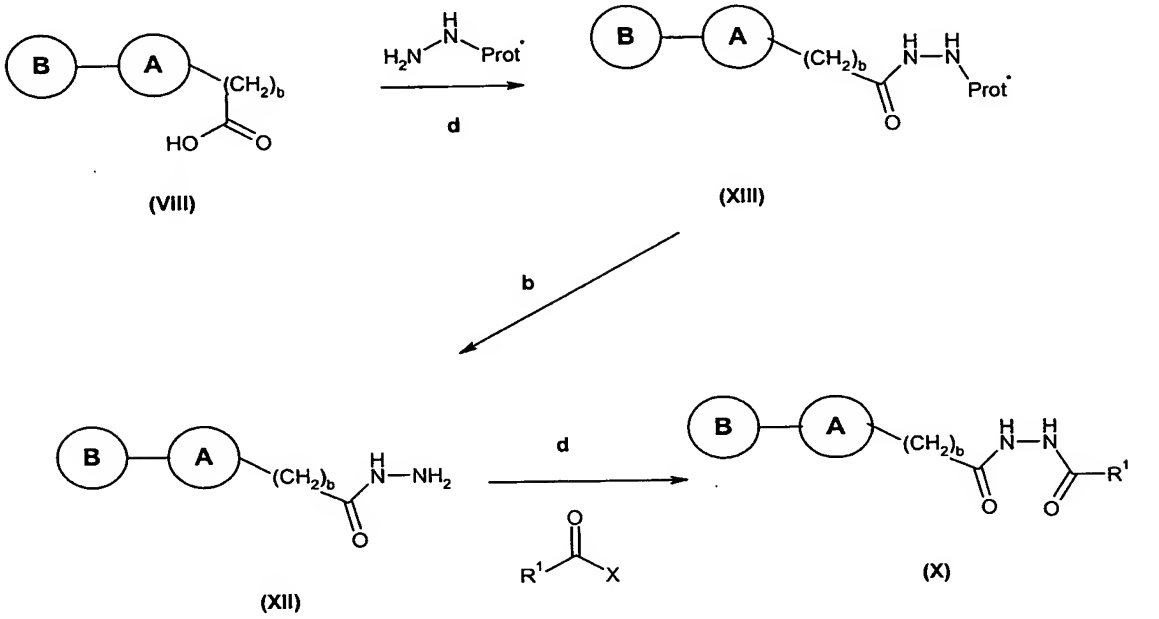
The preferred conditions are: acid chloride of acid **(VIII/VIII')** (generated in-situ), 2 eq. hydrazide, in DCM at rt. for 16 hours, or the carboxylic acid **(VIII/VIII')**, 1eq HOBT, 1 eq. WSCDI, 1.2 eq. hydrazide **(IX)** in dichloromethane at room temperature for 18 hours.

Step (e): Cyclisation of compound **(X/X')** is carried out under suitable dehydrating conditions, at elevated temperatures for up to 18 hours.

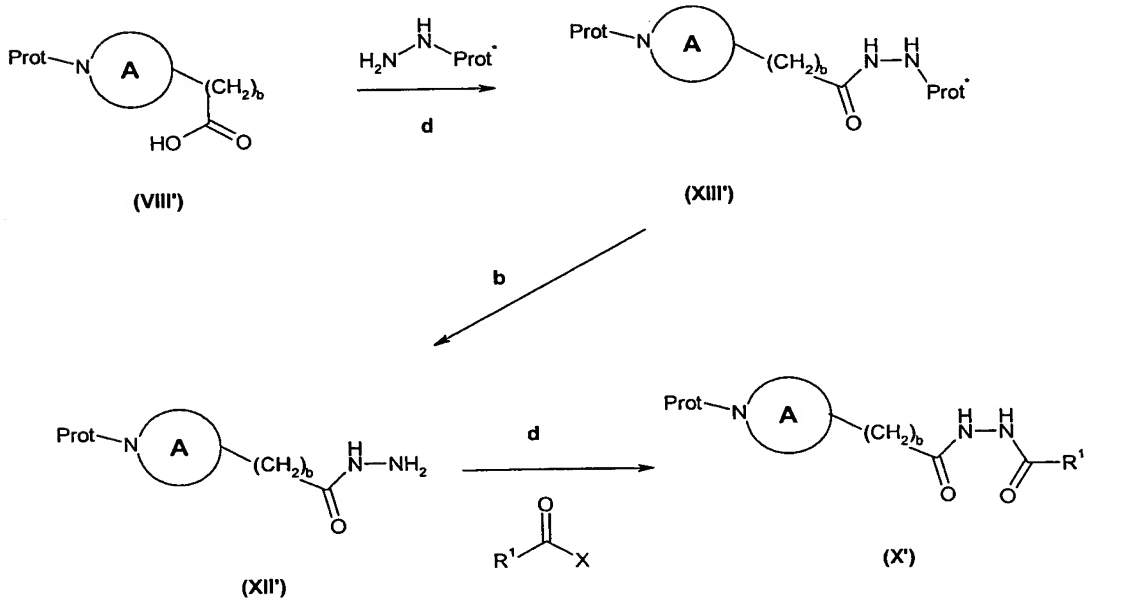
Typically, dehydrating agents such as polyphosphoric acid or phosphorous oxychloride are used at temperatures from 50 to 120°C for 5 minutes to 12 hours, optionally the reaction can be carried out under an inert atmosphere. Alternatively, the oxadiazole **(II/II')** may be prepared according to the method of Rigo et. al. Synth. Commun. 16(13), 1665, 1986.

Preferred conditions are: Phosphorous oxychloride at 100°C for 2 hours, or 1.8 eq. HMDS, cat. imidazole, cat. TBAF in chlorobenzene at 150°C for 18 hours.

Alternative routes to compound **(X/X')** are shown below in schemes 4.1 and 4.2:



Scheme 4.1



Scheme 4.2

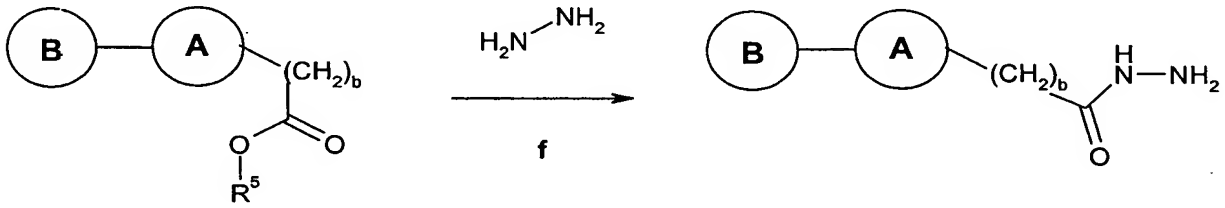
X is OH or Cl.

Carboxylic acid **(VIII/VIII')** and protected hydrazine, where prot* is typically Boc, may be coupled to give compound **(XIII/XIII')**, using the conditions described for the preparation of

(X/X') above, and then prot* is removed using standard methodology as described in **st p b**, to give **(XII/XII')**.

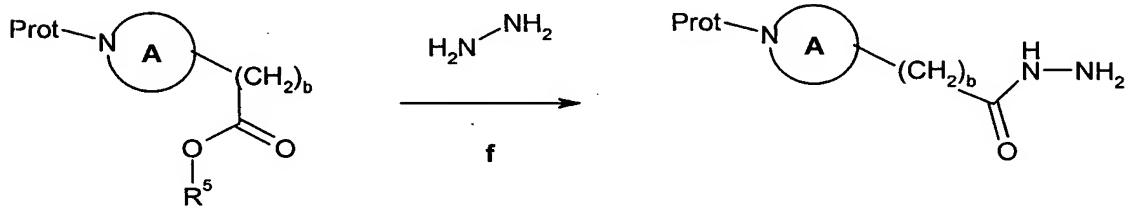
Compound **(X/X')** may then be obtained by the coupling of hydrazide **(XII/XII')** with a carboxylic acid or it's derivative ($R^1C(O)X$, where X is OH or Cl), under the conditions described previously for **step d**.

Alternative routes to compound **(XII/XII')** are shown below in schemes 5.1 and 5.2:



(XIV) **(XII)**

Scheme 5.1



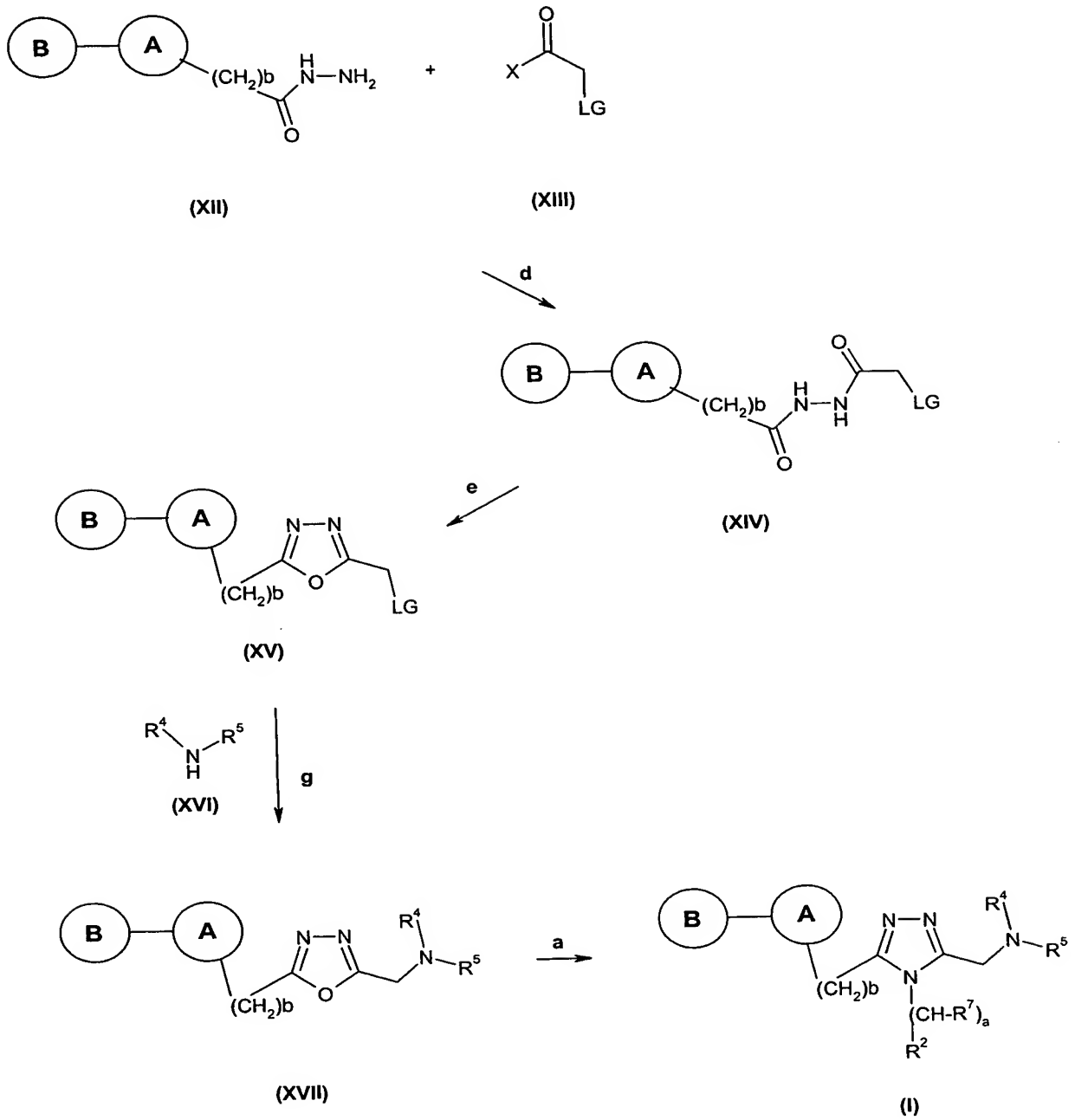
(XIV') **(XII')**

Scheme 5.2

Step (f): The ester **(XIV/XIV')** may be reacted with hydrazine in a suitable solvent, such as methanol at elevated temperature to provide the hydrazide **(XII/XII')**.

Preferred conditions: 3 eq. hydrazine, in methanol, at reflux for 18 hrs.

Compounds of the formula **(I/V')** may be prepared according to the routes described in Schemes 6.1 and 6.2:

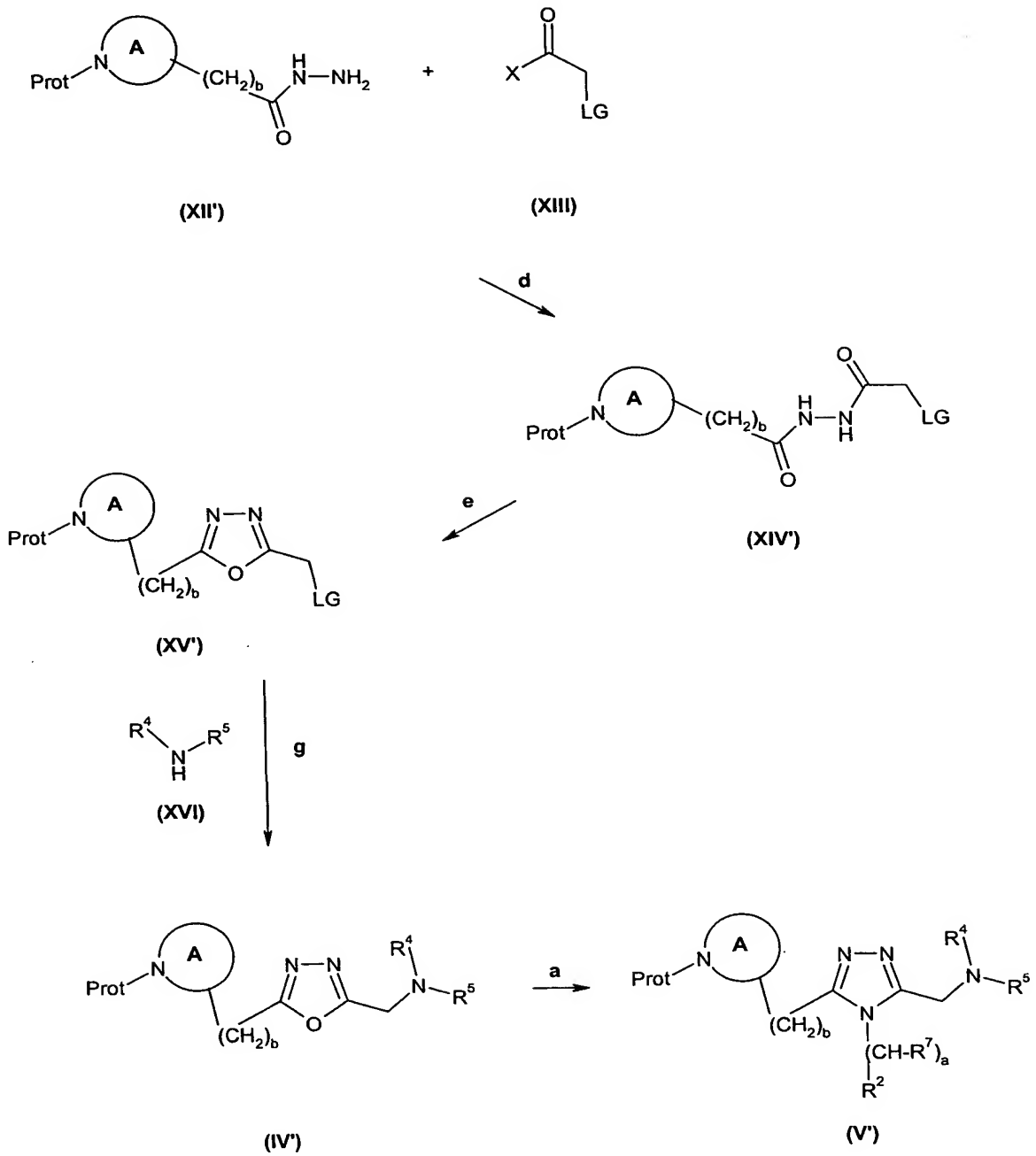


Scheme 6.1

X is OH or Cl.

LG is a leaving group, typically halo, and preferably chloro or bromo

5



Scheme 6.2

X is OH or Cl.

LG is a leaving group, typically halo, and preferably chloro or bromo

Compounds suitable for use as compound **(XIII)** and **(XVI)** are commercially available or are known in the literature.

Step (d): Coupling of compound **(XIII)** with hydrazide **(XII/XII')** may be carried out using standard methodology as outlined above.

Step (e): Dehydration and cyclisation of compound **(XIV/XIV')** to give oxadiazole **(XV/XV')** is achieved by the methodology outlined above.

Step (g): Compound **(XV/XV')** is reacted with amine **(XVI)** to give compound **(XVII/IV')** in the presence of an excess of base, such as triethylamine, Hünig's base or potassium carbonate as proton acceptor. In a suitable high boiling solvent such as Toluene or DMF at temperatures from 50°C to 100°C for 1 to 24 hours.
Alternatively a palladium catalysed cross-coupling reaction can be carried out using a suitable base (*t*-BuONa), a catalytic amount of a suitable additive such as tri n-butyl phosphine and a suitable palladium catalyst in toluene at reflux from 12 to 24 hours under an inert atmosphere.
Preferred conditions are: 1 eq. of amine, 2 eq. of potassium carbonate in DMF at 60°C for 3 hours.

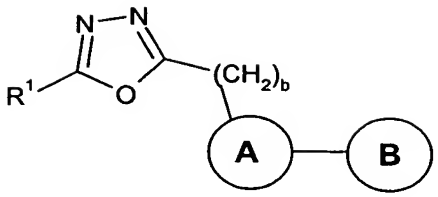
Step (a): Amination of compound **(XVII/IV')** to give compound **(I/V')** is carried out using the methodology outlined above.

It will be appreciated by those skilled in the art that when appropriate the order of steps **(a)** and **(g)** may be reversed.

Compounds **(V')** may be converted to compounds of formula **(I)** according to the reactions shown in scheme 2.

It will be apparent to those skilled in the art that sensitive functional groups may need to be protected and deprotected during synthesis of a compound of formula **(I/I')**. This may be achieved by conventional techniques, for example as described in "Protective Groups in Organic Synthesis" by T W Greene and P G M Wuts, John Wiley and Sons Inc, 1991.

In accordance with the present invention there is further provided a novel intermediate of formula **(II)**:



(II)

wherein R^1, rings A and B, and b are as defined above.

The compounds of the present invention are useful because they possess pharmacological activity in animals. In particular they are useful in the treatment of a number of conditions including aggression, Alzheimer's disease, anorexia nervosa, anxiety disorder, asthma, atherosclerosis, cardiac failure, cardiovascular disease, cataract, central nervous system disease, cerebrovascular ischemia, cirrhosis, cognitive disorder, Cushing's disease, depression, diabetes mellitus, dysmenorrhoea, edema, emesis, endometriosis, gastrointestinal disease, glaucoma, gynaecological disease, heart disease, hypertension, hyponatremia, ischemia, ischemic heart disease, lung tumor, micturition disorder, motion sickness, neoplasm, nephrotoxicity, non-insulin dependent diabetes, obesity, obsessive/compulsive disorder, ocular hypertension, premature labor, pulmonary disease, Raynaud's disease, renal disease, renal failure, male and female sexual dysfunction, sleep disorder, spinal cord injury, thrombosis, urogenital tract infection, urolithiasis. Particularly of interest is dysmenorrhoea.

Thus, according to another aspect of the invention, there is provided a method of treatment of dysmenorrhoea which comprises administering a therapeutically effective amount of a compound of the invention to a patient suffering from such a disorder. The use of the compounds as a medicament and the use of the compounds of the present invention in the manufacture of a medicament for the treatment of aggression, Alzheimer's disease, anorexia nervosa, anxiety disorder, asthma, atherosclerosis, cardiac failure, cardiovascular disease, cataract, central nervous system disease, cerebrovascular ischemia, cirrhosis, cognitive disorder, Cushing's disease, depression, diabetes mellitus, dysmenorrhoea, edema, emesis, endometriosis, gastrointestinal disease, glaucoma, gynaecological disease, heart disease, hypertension, hyponatremia, ischemia, ischemic heart disease, lung tumor, micturition disorder, motion sickness, neoplasm, nephrotoxicity, non-insulin dependent diabetes, obesity, obsessive/compulsive disorder,

ocular hypertension, premature labor, pulmonary disease, Raynaud's disease, renal disease, renal failure, male and female sexual dysfunction, sleep disorder, spinal cord injury, thrombosis, urogenital tract infection, urolithiasis, particularly dysmenorrhoea, are also provided.

The compounds of the present invention may be administered by any convenient route, for example orally, parenterally (e.g. intravenously, transdermally), or rectally. The daily dose required will, of course, vary with the particular compound used, the particular condition being treated and with the severity of that condition. However, in general a total daily dose of from about 0.01 to about 15 mg/kg of body weight, and preferably about 0.1 to about 5 mg/kg, is suitable, administered from 1 to 3 times daily. Oral administration is of particular interest.

The compounds of the present invention will generally be administered in the form of a pharmaceutical formulation. Thus, according to another aspect of the present invention, there is provided a pharmaceutical formulation comprising a compound of formula (I) in admixture with a pharmaceutically acceptable adjuvant, diluent or carrier. The pharmaceutical formulation is preferably in unit dose form. Such forms include solid dosage forms, for example tablets, pills, capsules, powders, granules and suppositories for oral, parenteral or rectal administration, and liquid dosage forms, for example sterile parenteral solutions or suspensions, suitably flavoured syrups, flavoured emulsions with edible oils such as cottonseed oil, sesame oil, coconut oil and peanut oil, and elixirs and similar pharmaceutical vehicles.

Solid formulations may be prepared by mixing the active ingredient with pharmaceutical carriers, for example conventional tabletting ingredients such as corn starch, lactose, sucrose, sorbitol, talc, stearic acid, magnesium stearate, dicalcium phosphate, gums and other diluents, for example water, to form a homogeneous preformulation formulation in which the active ingredient is uniformly dispersed so that it may be readily subdivided into equally effective unit dosage forms containing typically from 0.1 to 500mg of the active ingredient. The solid dosage forms may be coated or otherwise compounded to prolong the action of the formulation.

The compounds of the present invention may be tested in the screens set out below:

1.0 V_{1A} Filter Binding Assay

1.1 Membrane Preparation

Receptor binding assays were performed on cellular membranes prepared from CHO cells stably expressing the human V_{1A} receptor, (CHO-hV_{1A}). The CHO-hV_{1A} cell line was kindly provided under a licensing agreement by Marc Thibonnier, Dept. of Medicine, Case Western Reserve University School of Medicine, Cleveland, Ohio. CHO-hV_{1A} cells were routinely maintained at 37°C in humidified atmosphere with 5% CO_2 in DMEM/Hams F12 nutrient mix supplemented with 10 % fetal bovine serum, 2 mM L-glutamine, 15 mM HEPES and 400 µg/ml G418. For bulk production of cell pellets, adherent CHO-hV_{1A} cells were grown to confluency of 90-100% in 850 cm^2 roller bottles containing a medium of DMEM/Hams F12 Nutrient Mix supplemented with 10 % fetal bovine serum, 2 mM L-glutamine and 15 mM HEPES. Confluent CHO-hV_{1A} cells were washed with phosphate-buffered saline (PBS), harvested into ice cold PBS and centrifuged at 1,000 rpm. Cell pellets were stored at –80°C until use. Cell pellets were thawed on ice and homogenised in membrane preparation buffer consisting of 50 mM Tris-HCl, pH 7.4, 5 mM $MgCl_2$ and supplemented with a protease inhibitor cocktail, (Roche). The cell homogenate was centrifuged at 1000 rpm, 10 min, 4°C and the supernatant was removed and stored on ice. The remaining pellet was homogenised and centrifuged as before. The supernatants were pooled and centrifuged at 25,000 x g for 30 min at 4°C. The pellet was resuspended in freezing buffer consisting of 50 mM Tris-HCl, pH 7.4, 5 mM $MgCl_2$ and 20 % glycerol and stored in small aliquots at –80°C until use. Protein concentration was determined using Bradford reagent and BSA as a standard.

1.2 V_{1A} Filter binding

Protein linearity followed by saturation binding studies were performed on each new batch of membrane. Membrane concentration was chosen that gave specific binding on the linear portion of the curve. Saturation binding studies were then performed using various concentrations of [^{3}H]-arginine vasopressin, [^{3}H]-AVP (0.05 nM – 100 nM) and the K_d and B_{max} determined.

Compounds were tested for their effects on [^{3}H]-AVP binding to CHO-hV_{1A} membranes, (^{3}H-AVP; specific activity 65.5 Ci / mmol; NEN Life Sciences). Compounds were solubilised in dimethylsulfoxide (DMSO) and diluted to working concentration of 10% DMSO with assay buffer containing 50 mM Tris-HCL pH 7.4, 5 mM $MgCl_2$ and 0.05%

BSA. 25 µl compound and 25 µl [^{3}H]-AVP, (final concentration at or below K_d determined for membrane batch, typically 0.5 nM – 0.6 nM) were added to a 96-well round bottom polypropylene plate. The binding reaction was initiated by the addition of 200 µl membrane and the plates were gently shaken for 60 min at room temperature. The reaction was terminated by rapid filtration using a Filtermate Cell Harvester (Packard Instruments) through a 96-well GF/B UniFilter Plate which had been presoaked in 0.5% polyethyleneimine to prevent peptide sticking. The filters were washed three times with 1 ml ice cold wash buffer containing 50 mM Tris-HCL pH 7.4 and 5 mM $MgCl_2$. The plates were dried and 50 µl Microscint-0 (Packard instruments) was added to each well. The plates were sealed and counted on a TopCount Microplate Scintillation Counter (Packard Instruments). Non-specific binding (NSB) was determined using 1 µM unlabelled d(CH2)5Tyr(Me)AVP ([β-mercapto-β,β-cyclopentamethylenepropionyl,0-Me-Tyr^2,Arg^8]-vasopressin) (βMCPVP), (Sigma). The radioligand binding data was analysed using a four parameter logistic equation with the min forced to 0%. The slope was free fitted and fell between –0.75 and –1.25 for valid curves. Specific binding was calculated by subtracting the mean NSB cpm from the mean Total cpm. For test compounds the amount of ligand bound to the receptor was expressed as % bound = (sample cpm – mean NSB cpm)/specific binding cpm x100. The % bound was plotted against the concentration of test compound and a sigmoidal curve was fitted. The inhibitory dissociation constant (K_i) was calculated using the Cheng-Prusoff equation: $K_i=IC_{50}/(1+[L]/K_d)$ where [L] is the concentration of ligand present in the well and K_d is the dissociation constant of the radioligand obtained from Scatchard plot analysis.

2.0 V_{1A} Functional Assay; Inhibition of AVP / V_{1A}-R mediated Ca^{2+} mobilization by FLIPR (Fluorescent Imaging Plate Reader) (Molecular Devices)

Intracellular calcium release was measured in CHO-hV_{1A} cells using FLIPR, which allows the rapid detection of calcium following receptor activation. The CHO-hV_{1A} cell line was kindly provided under a licensing agreement by Marc Thibonnier, Dept. of Medicine, Case Western Reserve University School of Medicine, Cleveland, Ohio. CHO-V_{1A} cells were routinely maintained at 37°C in humidified atmosphere with 5% CO_2 in DMEM/Hams F12 nutrient mix supplemented with 10 % fetal bovine serum, 2 mM L-glutamine, 15 mM HEPES and 400 µg/ml G418. On the afternoon before the assay cells were plated at a density of 20,000 cells per well into black sterile 96-well plates with clear bottoms to allow cell inspection and fluorescence measurements from the bottom of each well. Wash

buffer containing Dulbecco's phosphate buffered saline (DPBS) and 2.5 mM probenecid and loading dye consisting of cell culture medium containing 4 µM Fluo-3-AM (dissolved in DMSO and pluronic acid),(Molecular Probes) and 2.5 mM probenecid was prepared fresh on the day of assay. Compounds were solubilised in DMSO and diluted in assay buffer consisting of DPBS containing 1% DMSO, 0.1% BSA and 2.5 mM probenecid. The cells were incubated with 100 µl loading dye per well for 1 hour at 37°C in humidified atmosphere with 5% CO_2. After dye loading the cells were washed three times in 100 µl wash buffer using a Denley plate washer. 100 µl wash buffer was left in each well. Intracellular fluorescence was measured using FLIPR. Fluorescence readings were obtained at 2s intervals with 50 µl of the test compound added after 30s. An additional 155 measurements at 2s intervals were then taken to detect any compound agonistic activity. 50 µl of arginine vasopressin (AVP) was then added so that the final assay volume was 200 µl. Further fluorescence readings were collected at 1s intervals for 120s. Responses were measured as peak fluorescence intensity (FI). For pharmacological characterization a basal FI was subtracted from each fluorescence response. For AVP dose response curves, each response was expressed as a % of the response to the highest concentration of AVP in that row. For IC_{50} determinations , each response was expressed as a % of the response to AVP. IC50 values were converted to a modified K_b value using the Cheng-Prusoff equation which takes into account the agonist concentration, [A], the agonist EC_{50} and the slope: $K_b=IC_{50}/(2+[A]/A_{50}]^n)^{1/n}-1$ where [A] is the concentration of AVP, A_{50} is the EC_{50} of AVP from the dose response curve and n=slope of the AVP dose response curve.

The compounds of the invention have the advantage that they are more potent, have a longer duration of action, have a broader range of activity, are more stable, have fewer side effects or are more selective, or have other more useful properties than the compounds of the prior art.

Thus the invention provides:

(i) a compound of formula **(I)** or a pharmaceutically acceptable salt or solvate thereof;

(ii) a process for the preparation of a compound of formula **(I)** or a pharmaceutically acceptable salt or solvate thereof;

(iii) a pharmaceutical formulation including a compound of formula **(I)** or a pharmaceutically acceptable salt or solvate thereof, together with a pharmaceutically acceptable excipients, diluent or carrier;

(iv) a compound of formula **(I)** or a pharmaceutically acceptable salt, solvate or composition thereof, for use as a medicament;

(v) the use of a compound of formula **(I)** or of a pharmaceutically acceptable salt, solvate or composition thereof, for the manufacture of a medicament for the treatment of aggression, Alzheimer's disease, anorexia nervosa, anxiety disorder, asthma, atherosclerosis, cardiac failure, cardiovascular disease, cataract, central nervous system disease, cerebrovascular ischemia, cirrhosis, cognitive disorder, Cushing's disease, depression, diabetes mellitus, dysmenorrhoea, edema, emesis, endometriosis, gastrointestinal disease, glaucoma, gynaecological disease, heart disease, hypertension, hyponatremia, ischemia, ischemic heart disease, lung tumor, micturition disorder, motion sickness, neoplasm, nephrotoxicity, non-insulin dependent diabetes, obesity, obsessive/compulsive disorder, ocular hypertension, premature labor, pulmonary disease, Raynaud's disease, renal disease, renal failure, male and female sexual dysfunction, sleep disorder, spinal cord injury, thrombosis, urogenital tract infection, urolithiasis;

(vi) use as in (v) where the disease or disorder is dysmenorrhoea;

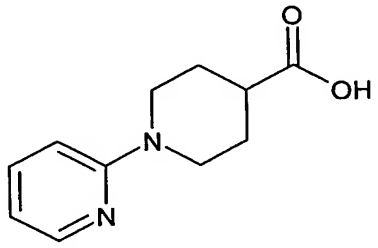
(vii) a method of treatment of a mammal to treat aggression, Alzheimer's disease, anorexia nervosa, anxiety disorder, asthma, atherosclerosis, cardiac failure, cardiovascular disease, cataract, central nervous system disease, cerebrovascular ischemia, cirrhosis, cognitive disorder, Cushing's disease, depression, diabetes mellitus, dysmenorrhoea, edema, emesis, endometriosis, gastrointestinal disease, glaucoma, gynaecological disease, heart disease, hypertension, hyponatremia, ischemia, ischemic heart disease, lung tumor, micturition disorder, motion sickness, neoplasm, nephrotoxicity, non-insulin dependent diabetes, obesity, obsessive/compulsive disorder, ocular hypertension, premature labor, pulmonary disease, Raynaud's disease, renal disease, renal failure, male and female sexual dysfunction, sleep disorder, spinal cord injury, thrombosis, urogenital tract infection, urolithiasis including treating said mammal with an effective amount of a compound of formula **(I)** or with a pharmaceutically acceptable salt, solvate or composition thereof;

(viii) a method as in (vii) where the disease or disorder is dysmenorrhoea;

(ix) a novel intermediate of the formula **(II)**;

The invention is illustrated by the following preparations and examples:

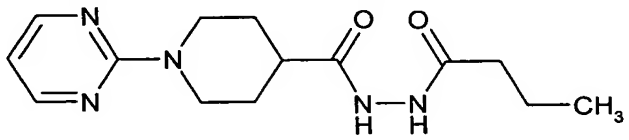
Preparation 1: 3,4,5,6-Tetrahydro-2H-[1,2']bipyridinyl-4-carboxylic acid



Sodium hydroxide solution (5M, 24.8 ml, 0.12 mol) was added drop wise to a solution of 3,4,5,6-tetrahydro-2H-[1,2']bipyridinyl-4-carboxylic acid ethyl ester (5.8 g, 24 mmol)(see reference Farmaco, 1993, 48(10), 1439) in 1,4-dioxane (100 ml). The mixture was stirred at room temperature for 72 hours and then evaporated under reduced pressure. The residue was purified by ion exchange chromatography on Dowex® 50 WX8 resin using methanol and ammonium hydroxide solution in water as eluant (gradient from 0:0:100 to 0:5:95 to 5:5:90). The material obtained was triturated with diethyl ether to give the title compound (4.42 g).

LCMS: *m/z* ES^+ 288 $[M+H]^+$

Preparation 2: 1-Pyrimidin-2-yl-piperidine-4-carboxylic acid N'-butyryl-hydrazide

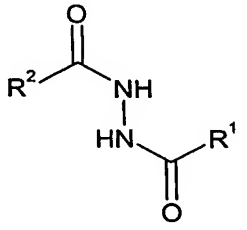


A mixture of 1-pyrimidin-2-yl-piperidine-4-carboxylic acid (3.0 g, 14.5 mmol)(see reference US 4826843), 1-hydroxybenzotriazole hydrate (1.96 g, 14.5 mmol) and 1-(3-dimethylaminopropyl-3-ethylcarbodiimide hydrochloride (2.78 g, 14.5 mmol) in dichloromethane (100 ml) was stirred for 10 minutes. Butyric acid hydrazide (1.78 g, 17.4 mmol) was added and the reaction mixture was stirred under a nitrogen atmosphere for 18 hours. The reaction mixture was diluted with dichloromethane (100 ml) and sodium hydrogen carbonate solution was added. The reaction mixture was concentrated under reduced pressure and the solid formed was isolated by filtration. The material obtained was dried under vacuum at 40°C to give the title compound (2.62 g).

LCMS: *m/z* ES^+ 314 $[M+Na]^+$

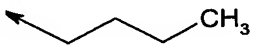
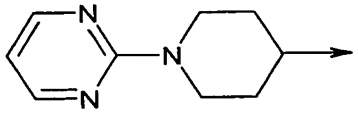
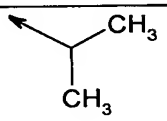
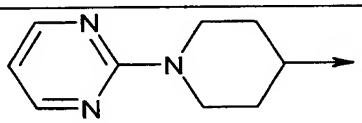
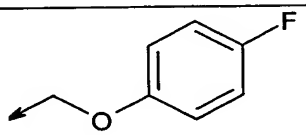
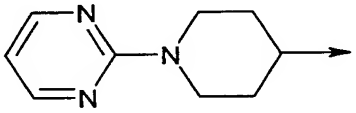
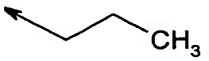
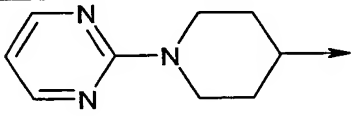
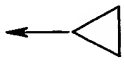
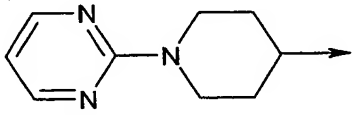
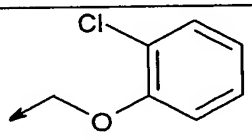
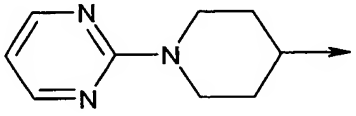
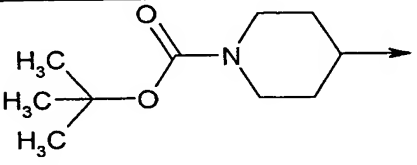
Preparations 3-11:

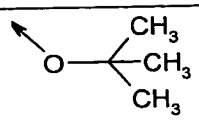
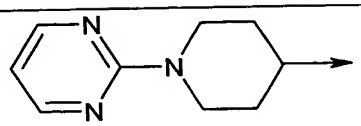
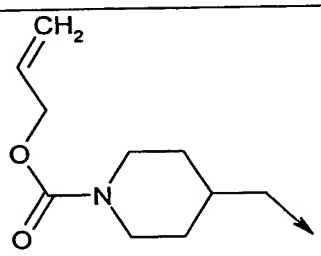
The compounds of the following tabulated Preparations (Table 2) of the general formula:



were prepared by a similar method to that of Preparation 2 using the appropriate carboxylic acid and hydrazide.

Table 2.

Preparation Number	R^1	R^2
3		
4		
5		
6		
7		
8		
9	CH_3	

10		
11^A	CH_3	

[A] See reference WO 9821210 (intermediate 96) for the starting carboxylic acid

Preparation 3:

LCMS: *m/z* ES^+ 328 $[M+Na]^+$

Preparation 4:

LCMS: *m/z* ES^+ 314 $[M+Na]^+$

Preparation 5:

LCMS: *m/z* ES^+ 396 $[M+Na]^+$

Preparation 6:

LCMS: *m/z* ES^+ 314 $[M+Na]^+$

Preparation 7:

^1H NMR (400MHz, DMSO-d_6): δ 0.69 (m, 4H), 1.58 (m, 6H), 2.93 (m, 2H), 4.62 (d, 2H), 6.59 (t, 1H), 8.34 (d, 2H), 9.67 (s, 1H), 9.94 (s, 1H).

Preparation 8:

^1H NMR (400MHz, DMSO-d_6): δ 1.50 (m, 2H), 1.80 (d, 2H), 2.90 (t, 2H), 4.60 (d, 2H), 4.70 (s, 2H), 6.60 (t, 1H), 6.95 (t, 2H), 7.10 (d, 1H), 7.20 (t, 1H), 7.40 (d, 1H), 8.30 (m, 2H), 10.0 (m, 2H).

Preparation 9:

^1H NMR (400MHz, DMSO-d_6): δ 1.39 (m, 11H), 1.64 (m, 2H), 1.81 (s, 3H), 2.35 (m, 1H), 2.74 (m, 2H), 3.92 (d, 2H), 9.88 (s, 2H).

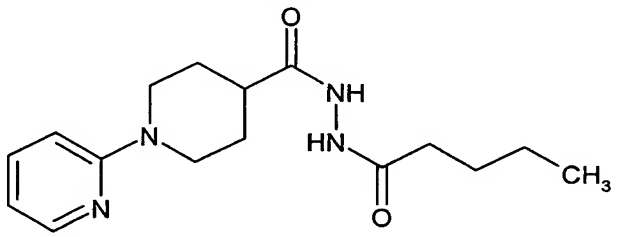
Preparation 10:

LCMS: *m/z* ES^- 320 $[M-H]^-$

Preparation 11:

LCMS: *m/z* ES^+ 306 $[M+Na]^+$

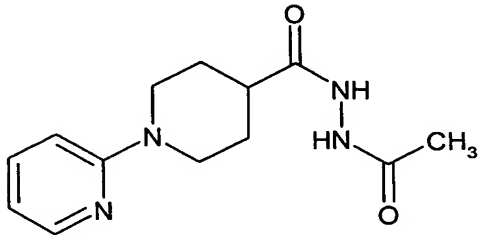
Preparation 12: 3,4,5,6-Tetrahydro-2H-[1,2']bipyridinyl-4-carboxylic acid N'-pentanoyl-hydrazide



The carboxylic acid from Preparation 1 (1.5 g, 7.3 mmol) was suspended in dichloromethane (40 ml) containing N,N-dimethylformamide (2 drops) and oxalyl chloride (1.27 ml, 14 mmol) in dichloromethane (5 ml) was added drop wise. The mixture was stirred for 5 hours at room temperature and then was evaporated under reduced pressure. The residue was suspended in hexane and evaporated (3x20 ml). The residue was dissolved in dichloromethane and cooled to 0°C and pentanoic acid hydrazide (1.7 g, 14.6 mmol) was added. 1-Methyl-pyrrolidin-2-one (1.6 ml, 14.6 mmol) in dichloromethane (10 ml) was added drop wise and the mixture was stirred at room temperature for 16 hours. The solvent was evaporated under reduced pressure and the residue was triturated with diethyl ether. The material obtained was dissolved in water and acidified to pH2 by addition of 2N hydrochloric acid. The acidic solution filtered and the filtrate was washed with ethyl acetate (3x20 ml) then basified with sodium carbonate. The solid formed was triturated with diethyl ether and isolated by filtration to give the title compound as a white solid (0.68 g).

LCMS: *m/z* ES^- 303 $[M-H]^-$

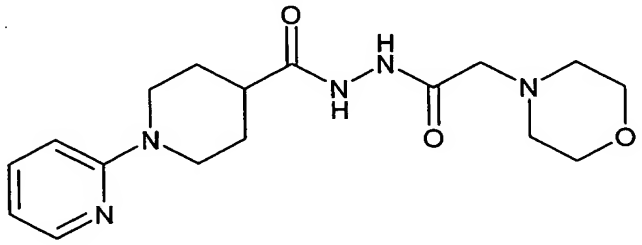
Preparation 13: 3,4,5,6-Tetrahydro-2*H*-[1,2']bipyridinyl-4-carboxylic acid N'-acetyl-hydrazide



The title compound was obtained from the carboxylic acid of Preparation 1 and acetyl hydrazide in 39% yield following the procedure described in Preparation 12.

APCI MS *m/z* 263 $[M+H]^+$

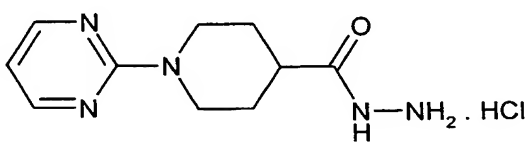
Preparation 14: 3,4,5,6-Tetrahydro-2*H*-[1,2']bipyridinyl-4-carboxylic acid N'-(2-morpholin-4-yl-acetyl)-hydrazide



The title compound was obtained from the carboxylic acid of Preparation 1 and morpholin-4-yl-acetic acid hydrazide (see reference Bull. Soc. Chim. Fr. 1962, 250) in 36% yield following the procedure described in Preparation 12.

^{1}H NMR (400MHz, $CDCl_3$): δ 1.87 (m, 2H), 1.96 (m, 2H), 2.60 (m, 5H), 2.59 (s, 2H), 3.01 (m, 2H), 3.75 (m, 4H), 4.35 (s, 2H), 6.63 (m, 1H), 6.72 (d, 1H), 7.32 (m, 1H), 8.14 (m, 1H), 8.81 (s, 1H), 9.26 (s, 1H).

Preparation 15: 1-Pyrimidin-2-yl-piperidine-4-carboxylic acid hydrazide hydrochloride

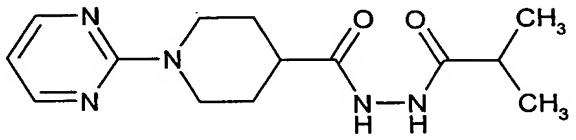


Hydrogen chloride solution in 1,4-dioxane (4M, 75 ml, 0.3 mol) was added to the hydrozone of Preparation 10 (5.5 g, 17 mmol) in methanol (20 ml) at 0°C. The mixture

was warmed to room temperature and then was stirred at room temperature for 16 hours. The solvent was evaporated under reduced pressure to give the title compound as a white solid (3 g)

^{1}H NMR (400MHz, DMSO-d_6): δ 1.57 (m, 2H), 1.83 (d, 2H), 2.70 (m, 1H), 3.08 (t, 2H), 4.64 (d, 2H), 6.78 (t, 1H), 8.47 (d, 2H), 11.35 (s, 1H).

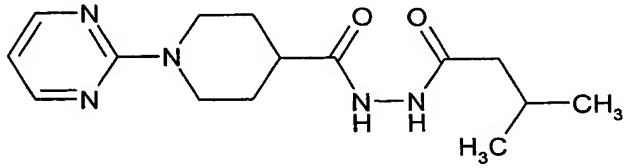
Preparation 16: 1-Pyrimidin-2-yl-piperidine-4-carboxylic acid N'-isobutyryl-hydrazide



The hydrazide of Preparation 15 (1.5 g, 4.6 mmol) was dissolved in N,N-dimethylformamide (15 ml) containing triethylamine (1.95 ml, 4.6 mmol) and isobutyryl chloride (0.53 ml, 5.1 mmol) was added. The mixture was stirred at room temperature for 16 hours and then at 60°C for 24 hours. The reaction mixture was cooled to room temperature and partitioned between dichloromethane and water. The organic solution was washed with sodium hydrogen carbonate solution, and brine, then dried over sodium sulphate and evaporated under reduced pressure. The residue was purified by chromatography on silica gel using methanol in dichloromethane as eluant (gradient from 0:100 to 4:96) to give the title compound (300 mg).

LCMS: *m/z* ES^+ 314 $[M+Na]^+$

Preparation 17: 1-Pyrimidin-2-yl-piperidine-4-carboxylic acid N'-(3-methyl-butyryl)-hydrazide



Diisopropylethylamine (10.2 ml, 56.8 mmol) and 3-methylbutyryl chloride (4.62 ml, 38 mmol) were added to a solution of hydrazinecarboxylic acid *tert*-butyl ester in dichloromethane (50 ml) and the mixture was stirred at room temperature for 18 hours. The reaction mixture was washed with water (100 ml) and the aqueous layer was extracted with dichloromethane (100 ml). The combined organic solutions were washed

with sodium hydrogen carbonate solution (50 ml) and brine (50 ml), dried over magnesium sulphate and evaporated under reduced pressure.

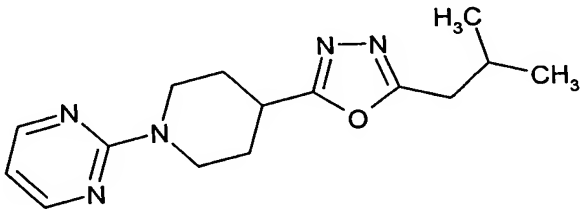
The residue was dissolved in dichloromethane (100 ml) and hydrogen chloride (4M solution in 1,4-dioxane) was added. The mixture was stirred at room temperature under a nitrogen atmosphere for 56 hours and the solvent was evaporated under reduced pressure.

The residue was added to a mixture of 1-pyrimidin-2-yl-piperidine-4-carboxylic acid (6.6 g, 31.7 mmol) (see reference US 4826843), 1-hydroxybenzotriazole hydrate (4.28 g, 31.7 mmol) and 1-(3-dimethylaminopropyl-3-ethylcarbodiimide hydrochloride (6.09 g, 31.7 mmol) in dichloromethane (50 ml). Diisopropylethylamine (17 ml, 95 mmol) was added and the mixture was stirred for 3 days. The solvent was evaporated and the residue was triturated with water and then with diethyl ether to give the title compound as a white solid (4.49 g).

^{1}H NMR (400MHz, DMSO-d_6): δ 0.90 (s, 6H), 1.50 (m, 2H), 1.74 (m, 2H), 1.99 (m, 2H), 2.99 (m, 4H), 4.61 (d, 2H), 6.59 (t, 1H), 8.34 (d, 2H), 9.59 (d, 1H), 9.67 (d, 1H).

LCMS: *m/z* ES$^-$ 304 [M-H]$^-$

Preparation 18: 2-[4-(5-Isobutyl-[1,3,4]oxadiazol-2-yl)-piperidin-1-yl]-pyrimidine



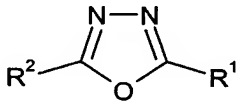
The hydrazide from preparation 17 (4.49 g, 14.7 mmol) was suspended in phosphorus oxychloride (50 ml) at 100°C under a nitrogen atmosphere for 2 hours. The mixture was cooled and the solvent was evaporated under reduced pressure and the last traces of phosphorus oxychloride were removed by toluene azeotrope. The residue was basified with sodium hydrogen carbonate solution and the aqueous solution was extracted with dichloromethane (2x100 ml). The combined organic layers were washed with brine, dried over magnesium sulphate and evaporated under reduced pressure to give the title compound as a brown oil (4.23 g).

^{1}H NMR (400MHz, DMSO-d_6): δ 0.92 (s, 6H), 1.64 (m, 2H), 2.04 (m, 3H), 2.71 (d, 2H), 3.18 (m, 2H), 3.28 (m, 1H), 4.54 (m, 2H), 6.60 (t, 1H), 8.34 (d, 2H).

LCMS: *m/z* ES$^+$ 288 $[M+H]^+$

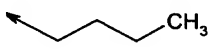
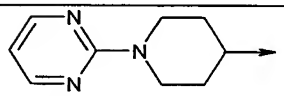
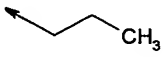
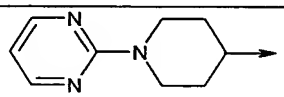
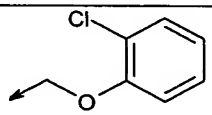
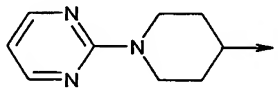
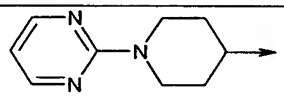
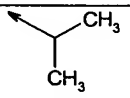
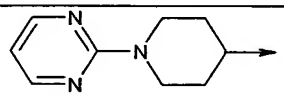
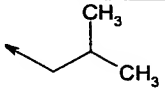
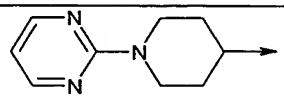
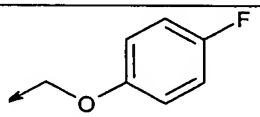
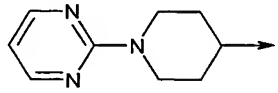
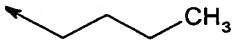
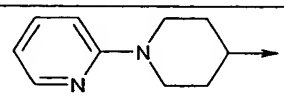
Preparations 19-30:

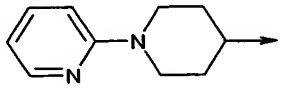
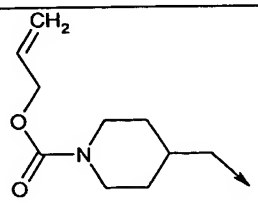
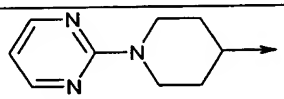
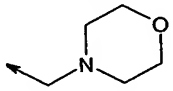
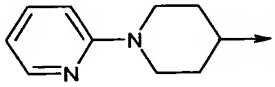
The compounds of the following tabulated Preparations (Table 3) of the general formula:



were prepared by a similar method to that of Preparation 18 using the appropriate hydrazide.

Table 3.

Preparation Number	R^1	R^2
19		
20		
21		
22		
23		
24		
25		
26		

27	CH_3	
28	CH_3	
29	CH_3	
30		

Preparation 19:

APCI MS *m/z* 288 $[M+H]^+$

Preparation 20:

LCMS: *m/z* ES^+ 274 $[M+H]^+$

Preparation 21:

LCMS: *m/z* ES^+ 272,274 $[M+H]^+$

Preparation 22:

^1H NMR (400MHz, $CDCl_3$): δ 1.08 (m, 4H), 1.86 (m, 2H), 2.11 (m, 2H), 3.18 (m, 3H), 4.72 (m, 2H), 6.50 (t, 1H), 8.33 (d, 2H).

Preparation 23:

LCMS: *m/z* ES^+ 296 $[M+Na]^+$

Preparation 24:

LCMS: *m/z* ES^+ 288 $[M+H]^+$

Preparation 25:

^1H NMR (400MHz, DMSO-d_6): δ 1.68 (m, 2H), 2.08 (m, 2H), 3.19 (m, 2H), 4.54 (m, 2H), 5.35 (s, 2H), 6.61 (t, 1H), 7.08 (m, 4H), 8.36 (d, 2H).

Preparation 26:

LCMS: *m/z* ES^+ 309 $[M+Na]^+$

Preparation 27:

LCMS: *m/z* ES^+ 267 $[M+Na]^+$

Preparation 28:

LCMS: *m/z* ES^+ 288 $[M+Na]^+$

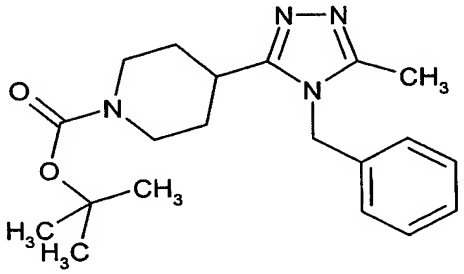
Preparation 29:

LCMS: *m/z* ES^+ 246 $[M+H]^+$

Preparation 30:

APCI MS *m/z* 330 $[M+H]^+$

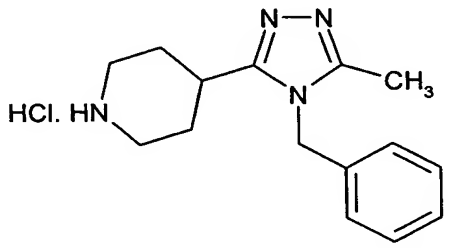
Preparation 31: 4-(4-Benzyl-5-methyl-4*H*-[1,2,4]triazol-3-yl)-piperidine-1-carboxylic acid tert-butyl ester



4-(5-Methyl-[1,3,4]oxadiazol-2-yl)-piperidine-1-carboxylic acid tert-butyl ester (5 g, 18.7 mmol)(see reference WO 0039125), benzylamine (2.5 ml, 22 mmol) and magnesium chloride (100 mg) were heated at 150°C for 1 hour, a further quantity of benzylamine (2.5 ml, 22 mmol) was added and the mixture was heated at 150°C for 4 hours. The reaction mixture was cooled to room temperature and the reaction mixture was purified by chromatography on silica gel using methanol in dichloromethane as eluant (3:97). The material isolated was triturated with diethyl ether to give the title compound as a white solid (4.69 g).

LCMS: *m/z* ES^+ 379 $[M+Na]^+$

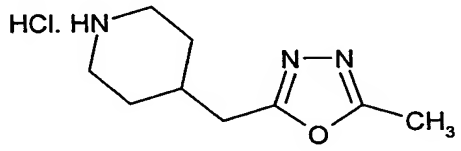
Preparation 32: 4-(4-Benzyl-5-methyl-4*H*-[1,2,4]triazol-3-yl)-piperidine hydrochloride



The protected piperidine of Preparation 31 (4.5 g, 12.6 mmol) was added to hydrogen chloride solution in 1,4-dioxane (4M, 80 ml) and the mixture was stirred at 15°C for 18 hours. The solvent was evaporated and the residue was triturated with diethyl ether to give the title compound as a white solid (3.25 g).

^{1}H NMR (400MHz, CF_3CO_2D): δ 2.03 (m, 2H), 2.32 (m, 2H), 2.76 (s, 3H), 3.27 (m, 2H), 3.47 (m, 1H), 3.66 (m, 2H), 5.46 (m, 2H), 7.32 (m, 5H), 11.40 (s, 2H).

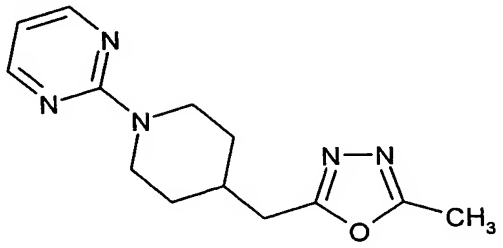
Preparation 33: 4-(5-Methyl-[1,3,4]oxadiazol-2-ylmethyl)-piperidine hydrochloride



The protected piperidine of Preparation 28 (934 mg, 3.5 mmol) was dissolved in tetrahydrofuran (20 ml) and tris(dibenzylideneacetone)dipalladium (65 mg, 0.18 mmol), 1,4-bis(diphenylphosphino)butane (75 mg, 0.18 mmol) and 2-thiobenzoic acid (1.9 g, 12.3 mmol) were added. The mixture was stirred at room temperature for 20 minutes and then was diluted with ethyl acetate (50 ml). The organic solution was acidified with 2M hydrochloric acid and was extracted with 2M hydrochloric acid (50 ml). The acidic solution was washed with ethyl acetate and then freeze dried to give the title compound as a white foam 900 mg).

^{1}H NMR (400MHz, DMSO-d_6): δ 1.46 (m, 2H), 1.79 (m, 2H), 2.04 (m, 1H), 2.45 (s, 3H), 2.79 (d, 2H), 2.85 (m, 2H), 3.20 (m, 2H), 8.76 (s, 1H), 9.05 (s, 1H).

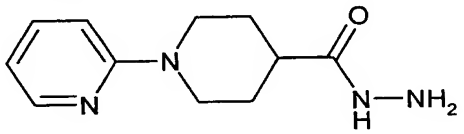
Preparation 34: 2-[4-(5-Methyl-[1,3,4]oxadiazol-2-ylmethyl)-piperidin-1-yl]-pyrimidine



The piperidine from Preparation 33 (766 mg, 3.52 mmol) was dissolved in N,N-dimethylformamide (10 ml) and 2-chloropyrimidine (510 mg, 3.52 mmol) and potassium carbonate (1.46 g, 10.6 mmol) were added. The mixture was heated to 100°C for 4 hours and then was cooled to room temperature. Ethyl acetate (50 ml) was added and the mixture was washed with water and brine, then dried over magnesium sulphate and evaporated under reduced pressure. The material obtained was recrystallised from ethyl acetate/methanol and the residue was purified by chromatography on silica gel using methanol in dichloromethane as eluant (gradient from 0:100 to 1:99) to give the title compound as a white solid (310 mg).

APCI MS *m/z* 260 $[M+H]^+$

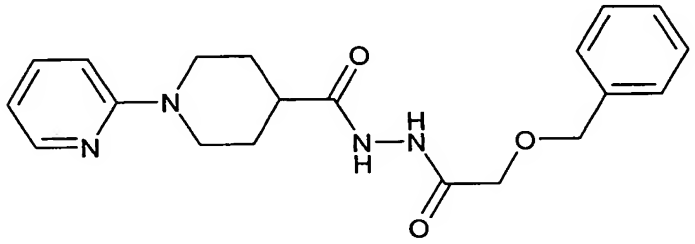
Preparation 35: 3,4,5,6-Tetrahydro-2*H*-[1,2']bipyridinyl-4-carboxylic acid hydrazide



3,4,5,6-Tetrahydro-2*H*-[1,2']bipyridinyl-4-carboxylic acid ethyl ester (1 g, 4.3 mmol)(see reference Farmaco, 1993, 48(10), 1439) was dissolved in methanol (20 ml) containing hydrazine hydrate (620 µl, 20 mmol) and was heated under reflux for 18 hours. The mixture was cooled to room temperature and evaporated under reduced pressure. The solid formed was triturated with propan-2-ol to give the title compound as a white solid (493 mg).

APCI MS *m/z* 221 $[M+H]^+$

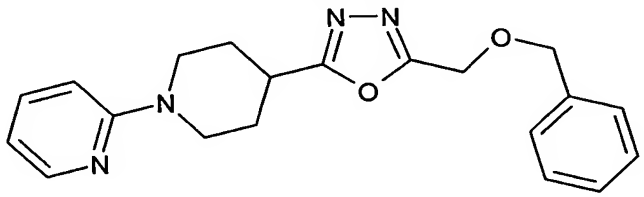
Preparation 36: 3,4,5,6-Tetrahydro-2*H*-[1,2']bipyridinyl-4-carboxylic acid N'-(2-benzyloxy-acetyl)-hydrazide



The hydrazide from preparation 35 (190 mg, 8.6 mmol) was suspended in dichloromethane containing 4-methymorpholine (136 µl, 1.5 mmol) and bezyloxyacetyl chloride (136 µl, 8.6 mmol) in dichloromethane (2 ml) was added drop wise. The mixture was stirred at room temperature for 1 hour and then was diluted with dichloromethane (50 ml). The organic solution was washed with water (50 ml) dried over magnesium sulphate ad evaporated under reduced pressure to give the title compound as a cream solid (285 mg).

APCI MS *m/z* 369 $[M+H]^+$

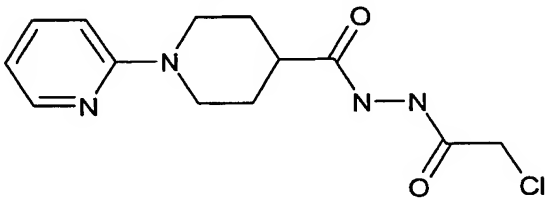
Preparation 37: 4-(5-Benzyloxymethyl-[1,3,4]oxadiazol-2-yl)-3,4,5,6-tetrahydro-2*H*-[1,2']bipyridinyl



The hydrazide from preparation 36 (260 mg, 0.7 mmol) was mixed with 1,1,1,3,3,3-hexamethyldisylazane (268 µl, 12.7 mmol), tetrabutyl ammonium fluoride trihydrate (22 mg, 0.07 mmol) and imidazole (20 mg) in chlorobenzene (5 ml). The mixture was heated at 150 °C for 16 hours and then evaporated under reduced pressure. The residue was purified by chromatography on silica gel using ethyl acetate as eluant to give the title compound (140 mg).

APCI MS *m/z* 350 $[M+H]^+$

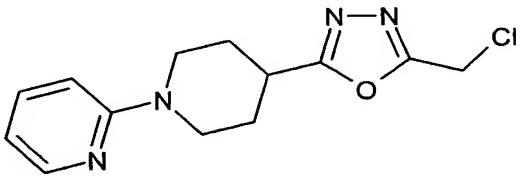
Preparation 38: 3,4,5,6-Tetrahydro-2*H*-[1,2']bipyridinyl-4-carboxylic acid N'-(2-chloro-acetyl)-hydrazide



The hydrazide of Preparation 35 (23.6 g, 0.11 mol) was suspended in dichloromethane (500 ml) and 4-methylmorpholine (17.7 ml, 0.16 mol) was added. The mixture was cooled using an ice bath and chloroacetyl chloride (12.8 ml, 0.16 mol) was added drop wise. The reaction was warmed to room temperature and was stirred for 3 hours. The solid formed was isolated by filtration washed with dichloromethane and diethyl ether and dried under vacuum to give the title compound (20.4 g).

LCMS: *m/z* ES^+ 297 $[M+H]^+$

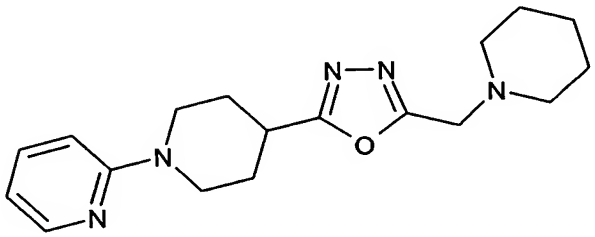
Preparation 39: 4-(5-Chloromethyl-[1,3,4]oxadiazol-2-yl)-3,4,5,6-tetrahydro-2*H*-[1,2']bipyridinyl



The hydrazide of Preparation 38 (20.4 g, 69 mmol) was suspended in phosphorus oxychloride (150 ml) at 100°C for 4 hours. The mixture was cooled and the solvent was evaporated under reduced pressure. The residue was dissolved in ethyl acetate and was added to water. The aqueous layer was basified by addition of solid sodium hydrogen carbonate and the phases were separated. The aqueous phase was extracted with ethyl acetate (x2) and the combined organic layers were dried over magnesium sulphate and evaporated under reduced pressure. The material isolated was triturated with diethyl ether to give the title compound as a beige solid (15 g).

^1H NMR (400MHz, CD_3OD): δ 1.91 (m, 2H), 2.19 (m, 2H), 3.14 (m, 2H), 3.30 (m, 1H), 4.29 (m, 2H), 4.86 (s, 2H), 6.69 (m, 1H), 6.89 (d, 1H), 7.58 (m, 1H), 8.08 (d, 1H)

Preparation 40: 4-(5-Piperidin-1-ylmethyl-[1,3,4]oxadiazol-2-yl)-3,4,5,6-tetrahydro-2*H*-[1,2']bipyridinyl

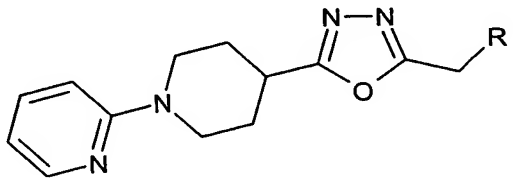


The chloromethyl compound of Preparation 39 (0.5 g, 1.8 mmol) was added to piperidine (0.18 ml, 1.8 mmol) and potassium carbonate (0.5 g, 3.6 mmol) in N,N-dimethylformamide (8 ml) and the mixture was heated at 60°C for 3 hours. The reaction mixture was evaporated under reduced pressure and the residue was partitioned between water and ethyl acetate. The organic solution was washed with water and then with 2N hydrochloric acid and the combined aqueous solutions were basified with solid sodium hydrogen carbonate. The aqueous mixture was extracted with ethyl acetate (x3) and the combined organic layers were dried over magnesium sulphate and evaporated under reduced pressure. The residue was purified by chromatography on silica gel using methanol and ammonium hydroxide in dichloromethane as eluant (2:0.25:98) to give the title compound as a pale pink solid (0.48 g).

LCMS: *m/z* ES^+ 328 $[M+H]^+$

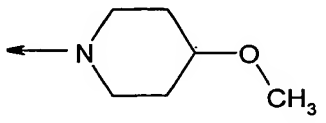
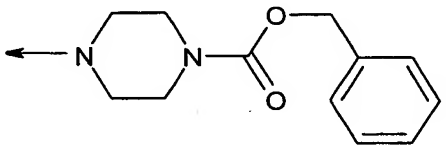
Preparations 41-43:

The compounds in Table 3 having the general formula:



were prepared by a similar method to that described in Preparation 40, using the product of Preparation 39 and an appropriate amine.

Table 3

Preparation number	R
41	
42	

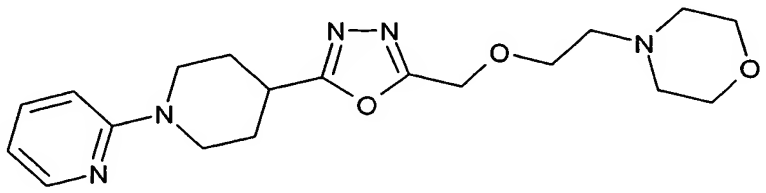
Preparation 41

^{1}H NMR (400MHz, CD_3OD): δ 1.61 (m, 2H), 1.91 (m, 4H), 2.18 (m, 2H), 2.39 (m, 2H), 2.80 (m, 2H), 3.12 (m, 2H), 3.30 (m, 5H), 3.82 (s, 2H), 4.29 (m, 2H), 6.66 (m, 1H), 6.87 (d, 1H), 7.57 (m, 1H), 8.08 (m, 1H)

Preparation 42

^{1}H NMR (400MHz, CD_3OD): δ 1.48 (m, 2H), 2.15 (m, 2H), 2.54 (m, 4H), 3.08 (m, 2H), 3.24 (m, 1H), 3.50 (s, 2H), 3.84 (s, 2H), 4.25 (m, 2H), 5.09 (s, 2H), 6.65 (m, 1H), 6.84 (d, 1H), 7.35 (m, 5H), 8.05 (m, 1H)

Preparation 43: 4-[5-(2-Morpholin-4-yl-ethoxymethyl)-[1,3,4]oxadiazol-2-yl]-3,4,5,6-tetrahydro-2H-[1,2']bipyridinyl

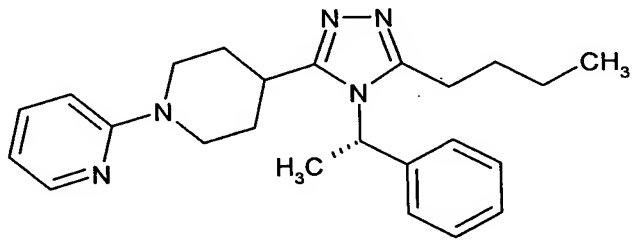


2-Morpholin-4-yl-ethanol (313 µl, 2.6 mmol) in tetrahydrofuran (2 ml) was added to a suspension of sodium hydride (60% in mineral oil, 103 mg, 2.6 mmol) in tetrahydrofuran

(2 ml) and the mixture was stirred at room temperature for 1 hour. A suspension of the chloromethyl compound of Preparation 39 (600 mg, 2.16 mmol) in tetrahydrofuran (10 ml) was added in 4 aliquots and the mixture was stirred at room temperature for 16 hours. Ethyl acetate (100 ml) was added and the solution was extracted with water (100 ml). The aqueous solution was washed with ethyl acetate (2x100 ml) and the combined organic layers were dried over magnesium sulphate and evaporated under reduced pressure. The residue was purified by chromatography on silica gel using methanol and ammonium hydroxide in dichloromethane as eluant (5:0.5:95) to give the title compound (500 mg).

^{1}H NMR (400MHz, CD_3OD): δ 1.85 (m, 2H), 2.17 (m, 2H), 2.52 (m, 4H), 2.62 (t, 2H), 3.11 (m, 2H), 3.30 (m, 1H), 3.68 (m, 4H), 3.73 (m, 2H), 4.28 (m, 2H), 4.72 (s, 2H), 6.66 (m, 1H), 6.85 (d, 1H), 7.55 (m, 1H), 8.06 (m, 1H)

Example 1: (S)-4-[5-Butyl-4-(1-phenyl-ethyl)-4*H*-[1,2,4]triazol-3-yl]-3,4,5,6-tetrahydro-2*H*-[1,2']bipyridinyl



The oxadiazole of Preparation 26 (149 mg, 0.52 mmol), anhydrous magnesium chloride (20 mg, 0.21 mmol) and *S*-(-)-1-phenylethylamine (120 µl, 1 mmol) were heated at 150°C for 18 hours. The reaction mixture was cooled to room temperature and dissolved in dichloromethane. The organic solution was washed with brine (3x20 ml) dried over sodium sulphate and evaporated under reduced pressure. The residue was purified by chromatography on silica gel using methanol in dichloromethane as eluant (4:96). The material obtained was co-evaporated with diethyl ether and then co-evaporated with methanol to give the title compound as a brown oil (90 mg).

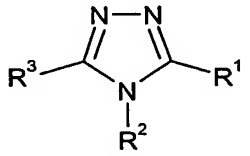
^{1}H NMR (400MHz, CD_3OD): δ 0.90 (t, 3H), 1.37 (m, 4H), 1.68 (m, 3H), 1.98 (m, 3H), 2.63 (m, 2H), 2.73 (m, 1H), 2.91 (m, 2H), 4.19 (d, 1H), 4.35 (d, 1H), 5.82 (q, 1H), 6.64 (m, 1H), 6.81 (d, 1H), 7.26 (d, 2H), 7.38 (m, 2H), 7.44 (m, 1H), 7.52 (m, 1H), 8.04 (d, 1H).

LCMS: *m/z* ES^+ 390 $[M+H]^+$

Found; C, 72.54; H, 8.11; N, 17.28; $C_{24}H_{31}N_5$ 0.5 H_2O requires; C, 72.33; H, 8.09; N, 17.57%.

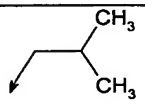
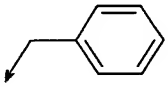
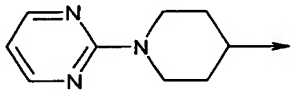
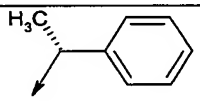
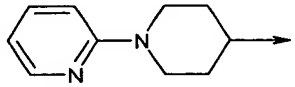
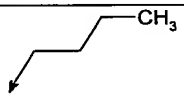
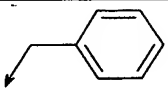
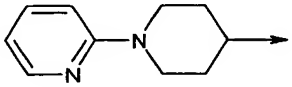
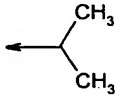
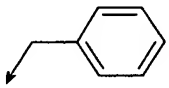
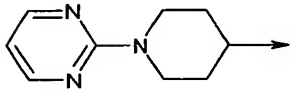
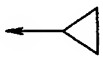
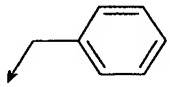
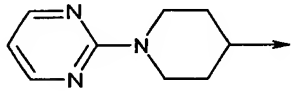
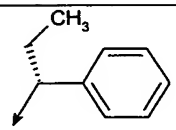
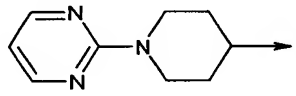
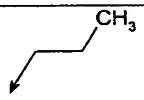
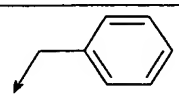
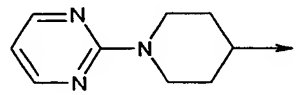
Examples 2-17:

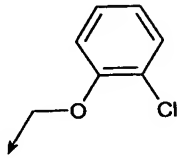
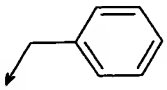
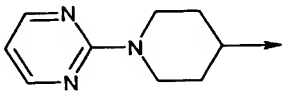
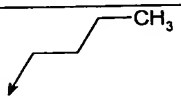
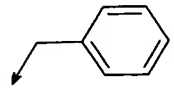
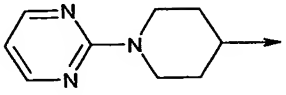
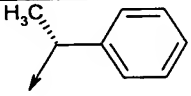
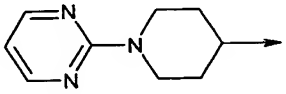
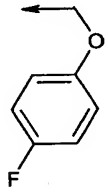
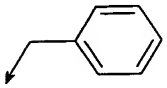
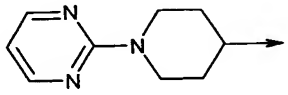
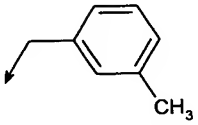
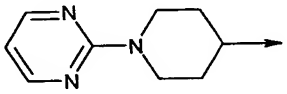
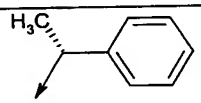
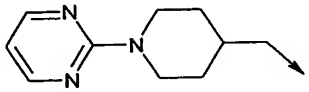
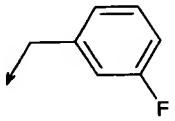
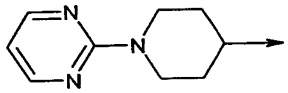
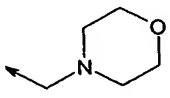
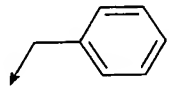
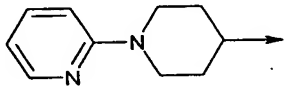
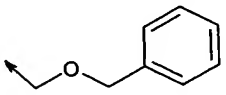
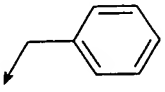
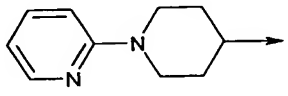
The compounds of the following tabulated examples (Table 1) of the general formula:



were prepared by a similar method to that of example 1 using the appropriate oxadiazole and amine.

Table1.

Example number	R^1	R^2	R^3
2^A			
3^B	CH_3		
4^C			
5^D			
6^E			
7^F	CH_3		
8^G			

Example number	R^1	R^2	R^3
9^H			
10^I			
11^F	CH_3		
12^J			
13^F	CH_3		
14^K	CH_3		
15^F	CH_3		
16^L			
17^M			

[A] see Preparation 18 for the oxadiazole

[B] see Preparation 30 for the oxadiazole

[C] see Preparation 26 for the oxadiazole

[D] see Preparation 23 for the oxadiazole

[E] see Preparation 22 for the oxadiazole

[F] see Preparation 29 for the oxadiazole
[G] see Preparation 20 for the oxadiazole
[H] see Preparation 21 for the oxadiazole
[I] see Preparation 19 for the oxadiazole
[J] see Preparation 25 for the oxadiazole
[K] see Preparation 34 for the oxadiazole
[L] see Preparation 30 for the oxadiazole
[M] see Preparation 37 for the oxadiazole

Example 2: 2-[4-(4-Benzyl-5-isobutyl-4*H*-[1,2,4]triazol-3-yl)-piperidin-1-yl]-pyrimidine

^{1}H NMR (400MHz, DMSO-d_6): δ 0.86 (d, 6H), 1.68 (m, 4H), 1.93 (m, 1H), 2.43 (d, 2H), 2.98 (m, 3H), 4.61 (d, 2H), 5.27 (s, 2H), 6.59 (m, 1H), 6.99 (d, 2H), 7.31 (m, 1H), 7.37 (m, 2H), 8.33 (d, 2H).

LRMS: m/z APCI 377$[M+H]^+$

Example 3: (*S*)-4-[5-Methyl-4-(1-phenyl-ethyl)-4*H*-[1,2,4]triazol-3-yl]-3,4,5,6-tetrahydro-2*H*-[1,2']bipyridinyl

^{1}H NMR (400MHz, $CDCl_3$): δ 1.72 (m, 3H), 1.93 (d, 3H), 2.08 (m, 4H), 2.23 (s, 3H), 2.80 (m, 2H), 2.93 (m, 1H), 4.33 (d, 1H), 4.40 (d, 2H), 5.54 (q, 1H), 6.60 (m, 1H), 6.66 (d, 1H), 7.12 (d, 1H), 7.28 (m, 3H), 7.46 (m, 1H), 8.15 (d, 1H).

LCMS: *m/z* ES^+ 348 $[M+H]^+$

Found; C, 70.57; H, 7.47; N, 19.49; $C_{21}H_{25}N_5$ 0.5 H_2O requires; C, 70.76; H, 7.35; N, 19.65%.

Example 4: 4-[4-Benzyl-5-butyl-4*H*-[1,2,4]triazol-3-yl]-3,4,5,6-tetrahydro-2*H*-[1,2']bipyridinyl

^{1}H NMR (400MHz, $CDCl_3$): δ 0.88 (t, 3H), 1.40 (m, 2H), 1.70 (m, 2H), 1.85 (m, 2H), 2.07, (m, 2H), 2.67 (m, 2H), 1.79 (m, 1H), 2.89 (m, 2H), 4.34 (d, 2H), 5.11 (s, 2H), 6.59 (m, 1H), 6.65 (d, 1H), 7.36 (m 3H), 7.44 (m, 1H), 8.15 (d, 1H).

LCMS: *m/z* ES^+ 398 $[M+Na]^+$

Found; C, 73.40; H, 7.82; N, 18.59; $C_{23}H_{29}N_5$ requires; C, 73.57; H, 7.78; N, 18.65%.

Example 5: 2-[4-(4-Benzyl-5-isopropyl-4*H*-[1,2,4]triazol-3-yl)-piperidin-1-yl]-pyrimidine

^1H NMR (400MHz, $CDCl_3$): δ 1.33 (d, 6H), 1.81 (m, 2H), 1.99 (m, 2H), 2.90 (m, 4H), 4.75 (m, 2H), 5.13 (s, 2H), 6.45 (t, 1H), 6.94 (d, 2H), 7.34 (m 3H), 8.27 (d, 2H).

LCMS: *m/z* ES^- 361 $[M-H]^-$

Example 6: 2-[4-(4-Benzyl-5-cyclopropyl-4*H*-[1,2,4]triazol-3-yl)-piperidin-1-yl]-pyrimidine

HPLC Waters Xterra™ C18 5μm 19x100mm 50:50 (H_2O+0.1% diethylamine/acetonitrile), 18 ml/min. 1.04 min

LRMS: m/z APCI 353$[M+H]^+$

Example 7: (*S*)-2-{4-[5-Methyl-4-(1-phenyl-propyl)-4*H*-[1,2,4]triazol-3-yl)-piperidin-1-yl]-pyrimidine

^1H NMR (400MHz, $CDCl_3$): δ 0.92 (m, 2H), 1.10 (m, 2H), 1.60 (m, 1H), 1.80 (m, 2H), 2.99 (m, 2H), 4.78 (m, 2H), 5.22 (s, 2H), 6.46 (t, 1H), 7.01 (d, 2H), 7.37 (m, 3H), 8.27 (d, 2H).

APCI MS *m/z* 361 $[M+H]^+$

Example 8: 2-[4-(4-Benzyl-5-propyl-4*H*-[1,2,4]triazol-3-yl)-piperidin-1-yl]-pyrimidine

^1H NMR (400MHz, $CDCl_3$): δ 0.99 (t, 3H), 1.43 (d, 1H), 1.91 (m, 3H), 2.19 (m, 1H), 2.29 (s, 3H), 2.54 (m, 1H), 2.77 (m 2H), 3.92 (m, 1H), 4.72 (d, 1H), 4.81 (d, 1H), 5.26 (m, 1H), 6.44 (t, 1H), 7.13 (d, 2H), 7.35 (m, 3H), 8.28 (d, 2H).

LCMS: *m/z* ES^+ 363 $[M+H]^+$

Example 9: 2-{4-[4-Benzyl-5-(2-chloro-phenoxymethyl)-4*H*-[1,2,4]triazol-3-yl]-piperidin-1-yl}-pyrimidine

^{1}H NMR (400MHz, $CDCl_3$): δ 0.95 (t, 3H), 1.78 (m, 4H), 1.96 (m, 2H), 2.60 (t, 2H), 2.79 (m, 1H), 2.94 (t, 2H), 4.78 (d, 2H), 5.09 (s, 2H), 6.44 (t, 1H), 6.95 (d, 2H), 7.34 (m, 3H), 8.28 (d, 2H).

LCMS: *m/z* ES^+ 363 $[M+H]^+$

Example 10: 2-[4-(4-Benzyl-5-butyl-4*H*-[1,2,4]triazol-3-yl)-piperidin-1-yl]-pyrimidine

^{1}H NMR (400MHz, $CDCl_3$): δ 0.84 (m, 2H), 2.01 (m, 2H), 2.93 (m, 3H), 4.80 (d, 2H), 5.17 (s, 2H), 5.40 (s, 2H), 6.48 (t, 1H), 6.93 (m, 1H), 7.04 (m, 2H), 7.11 (d, 1H), 7.20 (m, 1H), 7.33 (m, 3H), 8.30 (d, 2H).

LCMS: *m/z* ES^+ 461, 463 $[M+H]^+$

Example 11: (*S*)-2-{4-[5-Methyl-4-(1-phenyl-ethyl)-4*H*-[1,2,4]triazol-3-yl)-piperidin-1-yl]-pyrimidine

^{1}H NMR (400MHz, $CDCl_3$): δ 0.89 (t, 3H), 1.38 (q, 2H), 1.70 (m, 2H), 1.80 (d, 2H), 1.99 (m, 2H), 2.63 (t, 2H), 2.80 (m, 1H), 2.94 (m, 2H), 4.76 (d, 2H), 5.10 (s, 2H), 6.46, (t, 1H), 6.95 (d, 2H), 7.33 (m, 3H), 8.27 (d, 2H).

APCI MS *m/z* 377 $[M+H]^+$

Example 12: 2-{4-[4-Benzyl-5-(4-fluoro-phenoxymethyl)-4*H*-[1,2,4]triazol-3-yl]-piperidin-1-yl}-pyrimidine

^{1}H NMR (400MHz, $CDCl_3$): δ 1.79 (m, 2H), 1.99 (m, 2H), 2.90 (m, 3H), 4.77 (m, 2H), 5.11 (s, 2H), 5.28 (s, 2H), 6.48 (t, 1H), 6.83 (m, 2H), 6.90 (m, 2H), 6.99 (m, 2H), 7.31 (m, 3H), 8.26 (d, 2H).

LCMS: *m/z* ES^+ 467 $[M+Na]^+$

Example 13: 2-{4-[5-Methyl-4-(3-methyl-benzyl)-4*H*-[1,2,4]triazol-3-yl)-piperidin-1-yl]-pyrimidine

LCMS: *m/z* ES^+ 349 $[M+H]^+$

HPLC Phenomenex C_8 5µm 10x150 mm, 50:50 (H_2O+0.1% diethylamine/acetonitrile), 8 ml/min. 214 nM 4.41 min.

Example 14: (*S*)-2-{4-[5-Methyl-4-(1-phenyl-ethyl)-4*H*-[1,2,4]triazol-3-ylmethyl]-piperidin-1-yl}-pyrimidine

^1H NMR (400MHz, $CDCl_3$): δ 1.19 (m, 2H), 1.80 (m, 1H), 1.88 (m, 4H), 2.10 (m, 1H), 2.26 (s, 3H), 2.50 (m, 1H), 2.63 (m, 1H), 2.82 (m, 2H), 4.70 (m, 2H), 5.47 (m, 1H), 6.42 (t, 1H), 7.09 (m, 2H), 7.35 (m, 3H), 8.26 (d, 2H).

LCMS: *m/z* ES^- 385 $[M-H]^-$

Example 15: 2-{4-[4-(3-Fluoro-benzyl)-5-methyl-4*H*-[1,2,4]triazol-3-yl)-piperidin-1-yl]-pyrimidine

HPLC Phenomenex C_8 5µm 10x150 mm, 50:50 (H_2O+0.1% diethylamine/acetonitrile), 8 ml/min. 214 nM, 1.24 min.

LRMS: m/z APCI 353$[M+H]^+$

Example 16: 4-(4-Benzyl-5-morpholin-4-ylmethyl-4*H*-[1,2,4]triazol-3-yl)-3,4,5,6-tetrahydro-2*H*-[1,2']bipyridinyl

^1H NMR (400MHz, CD_3OD): δ 1.74 (m, 2H), 1.88 (m, 2H), 2.21 (m, 4H), 2.82 (m, 2H), 2.99 (m, 1H), 3.53 (m, 4H), 3.62 (s, 2H), 4.29 (m, 2H), 6.63 (m, 1H), 6.80 (d, 1H), 7.13 (d, 2H), 7.38 (m, 3H), 7.54 (m, 1H), 8.06 (d, 1H).

LRMS: m/z APCI 419$[M+H]^+$

Found; C, 68.53; H, 7.25; N, 19.79; C24H30N6O requires C, 68.87; H, 7.22; N, 20.08%.

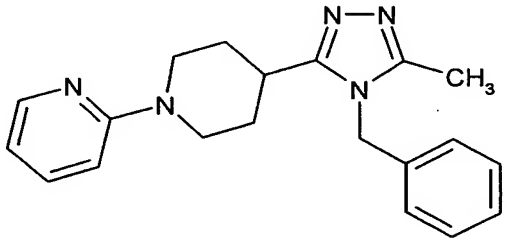
Example 17: 4-(4-Benzyl-5-benzyloxymethyl-4*H*-[1,2,4]triazol-3-yl)-3,4,5,6-tetrahydro-2*H*-[1,2']bipyridinyl

^{1}H NMR (400MHz, CD_3OD): δ 1.68 (m, 2H), 1.84 (m, 2H), 2.81 (m, 2H), 2.98 (m, 1H), 4.26 (m, 2H), 4.53 (s, 2H), 4.67 (s, 2H), 5.35 (s, 2H), 6.64 (m, 1H), 6.81 (d, 1H), 7.13 (m, 2H), 7.31 (m, 8H), 7.54 (m, 1H), 8.03 (d, 1H).

LRMS: m/z APCI 440$[M+H]^+$

Found; C, 72.67; H, 6.67; N, 15.87; $C_{27}H_{29}N_5O \cdot 0.3\ H_2O$ requires; C, 72.88; H, 6.71; N, 15.74%.

Example 18: 4-(4-Benzyl-5-methyl-4*H*-[1,2,4]triazol-3-yl)-3,4,5,6-tetrahydro-2*H*-[1,2']bipyridinyl



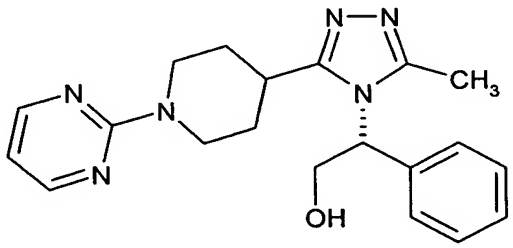
The piperidine from preparation 29 (200 mg, 0.6 mmol) was mixed with 2-chloropyridine (60 µl, 0.6 mmol) and diisopropyl ethylamine (310 µl, 1.8 mmol) in N-methylpyrrolidinone (5 ml) and the mixture was heated to 140°C for 18 hours. The reaction mixture was cooled to room temperature, added to water (150 ml) and acidified with 2N hydrochloric acid. The aqueous solution was washed with ethyl acetate (3x100 ml), basified with solid sodium carbonate, filtered through Hyflo Super Cel® and extracted with ethyl acetate (3x20 ml). The combined organic layers were dried over sodium sulphate and evaporated under reduced pressure. The residual orange oil was purified by chromatography on silica gel using methanol in dichloromethane as eluant (6:94) to give the title compound as an orange oil (10 mg).

^{1}H NMR (400MHz, CD_3OD): δ 1.83 (m, 4H), 2.38 (s, 3H), 2.89 (m, 2H), 3.02 (m, 1H), 4.30 (d, 2H), 5.35 (s, 2H), 6.64 (m, 1H), 7.08 (d, 2H), 7.20 (m, 3H), 7.34 (m, 1H), 7.60 (m, 1H), 8.06 (d, 1H).

s

LCMS: *m/z* ES^+ 356 $[M+Na]^+$

Example 19: (*R*)-2-[3-Methyl-5-(1-pyrimidin-2-yl-piperidin-4-yl)-[1,2,4]triazol-4-yl]-2-phenyl-ethanol



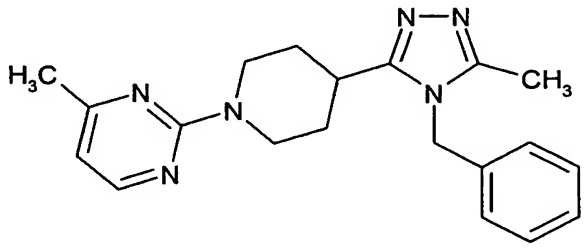
4-(5-Methyl-[1,3,4]oxadiazol-2-yl)-piperidine-1-carboxylic acid tert-butyl ester (1 g, 3.7 mmol)(see reference WO 0039125), (R)-(-)-2-amino-2-phenylethanol (617 mg, 4.4 mmol) and 4-methylphenylsulphonic acid (20 mg) in Xylene (10 ml) were heated under reflux for 48 hours. The solvent was evaporated under reduced pressure and the residue was partitioned between dichloromethane and sodium hydrogen carbonate solution. The aqueous layer was extracted with dichloromethane and the combined organic layers were washed with brine, dried over magnesium sulphate and evaporated under reduced pressure. The residue was purified by chromatography on silica gel using methanol and ammonium hydroxide in dichloromethane as eluant (10:1:90). The material obtained was dissolved in 4M hydrogen chloride solution in 1,4-dioxane and the mixture was stirred at 15°C for 2 hours. The solvent was evaporated under reduced pressure and the residue was triturated with diethyl ether.

The material obtained was mixed with 2-bromopyrimidine (170 mg, 1.1 mmol) and potassium carbonate (308 mg, 2.2 mmol) in N,N-dimethylformamide (1 ml) and was heated at 50°C for 4 hours. The reaction mixture was cooled to room temperature and was partitioned between water and dichloromethane. The aqueous phase was extracted with dichloromethane and the combined organic phases were washed with brine, dried over magnesium sulphate and evaporated under reduced pressure. The residue was pre-adsorbed onto a small quantity of silica gel and then was purified by chromatography on silica gel using methanol and ammonium hydroxide in ethyl acetate as eluant (9:0.1:91) to give the title compound as a white solid (46 mg).

^1H NMR (400MHz, $CDCl_3$): δ 1.75 (m, 1H), 1.83 (m, 3H), 2.15 (s, 3H), 2.70 (t, 1H), 2.84 (m, 2H), 4.01 (t, 1H), 4.40 (m, 1H), 4.70 (m, 2H), 5.12 (s, 1H), 5.42 (m, 1H), 6.38 (d, 1H), 7.06 (d, 2H), 7.29 (m, 3H), 8.20 (d, 2H).

LCMS: *m/z* ES^+ 365 $[M+Na]^+$

Example 20: 2-[4-(4-Benzyl-5-methyl-4*H*-[1,2,4]triazol-3-yl)-piperidin-1-yl]-4-methyl-pyrimidine

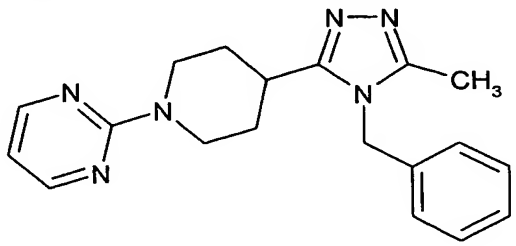


The piperidine of Preparation 29 (100 mg, 0.39 mmol) was mixed with 2-bromo-4-methylpyrimidine (88 mg, 0.51 mmol) and potassium carbonate (80 mg, 0.6 mmol) in N,N-dimethylformamide (0.5 ml) and was heated at 50°C for 4 hours. The reaction mixture was cooled to room temperature and was partitioned between water and dichloromethane. The aqueous phase was extracted with dichloromethane and the combined organic phases were washed with brine, dried over magnesium sulphate and evaporated under reduced pressure. The residue was triturated with diethyl ether and the material obtained was purified by chromatography on silica gel using methanol in dichloromethane as eluant (10:90). The isolated solid was triturated with diethyl ether to give the title compound as a white solid (30 mg).

^{1}H NMR (400MHz, $CDCl_3$): δ 1.76 (m, 2H), 1.92 (m, 2H), 2.06 (s, 3H), 2.10 (s, 3H), 2.77 (m, 1H), 4.76 (m, 2H), 5.05 (s, 2H), 6.30 (d, 1H), 6.95 (d, 2H), 7.30 (m, 3H), 8.10 (d, 1H).

Found; C, 68.76; H, 7.04; N, 24.03; $C_{20}H_{24}N_6$ requires; C, 68.94; H, 6.94; N, 24.12%.

Example 21: 2-[4-(4-Benzyl-5-methyl-4*H*-[1,2,4]triazol-3-yl)-piperidin-1-yl]-pyrimidine



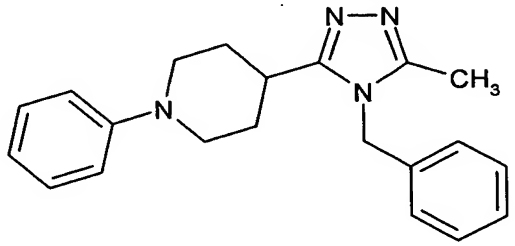
The title compound was obtained from the piperidine of Preparation 29 (100 mg, 0.39 mmol) and 2-bromopyrimidine in 39% yield following the procedure described in Example 20.

^{1}H NMR (400MHz, $CDCl_3$): δ 1.78 (d, 2H), 1.98 (q, 2H), 2.32 (s, 3H), 2.78 (m, 1H), 2.92 (m, 2H), 4.75 (d, 2H), 5.05 (s, 2H), 6.42 (t, 1H), 6.93 (d, 2H), 7.32 (m, 3H), 8.24 (d, 2H).

LCMS: *m/z* ES^+ 357 $[M+Na]^+$

Found; C, 67.61; H, 6.69; N, 24.64; $C_{19}H_{22}N_6$ 0.2 H_2O requires; C, 67.57; H, 6.68; N, 24.86%.

Example 22: 4-(4-Benzyl-5-methyl-4*H*-[1,2,4]triazol-3-yl)-1-phenyl-piperidine

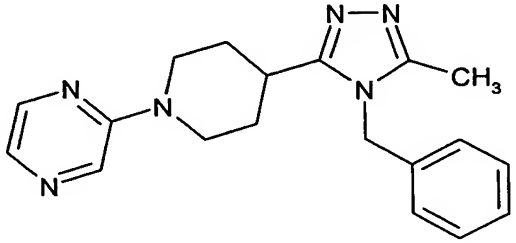


3-Brombenzene (80 µl, 0.75 mmol) was added to a mixture of the piperidine from Preparation 29 (250 mg, 0.75 mmol), sodium *tert*-butoxide (250 mg, 2.6 mmol) (+/-) 2,2'-bis(diphenylphosphino)-1,1'-binaphthyl, (19 mg, 0.03 mmol) and tris(dibenzylideneacetone)dipalladium (14 mg, 0.15 mmol) in toluene (x ml) and the mixture was stirred at 70°C for 4 hours. Diisopropylamine (260 µl, 2.6 mmol) and further quantities of 2,2'-bis(diphenylphosphino)-1,1'-binaphthyl (19 mg, 0.03 mmol) and tris(dibenzylideneacetone)dipalladium (14 mg, 0.15 mmol) were added and the reaction mixture was stirred at 70°C for a further 4 hours. The reaction mixture was cooled to room temperature and evaporated under reduced pressure. The residue was partitioned between sodium carbonate solution (20 ml) and ethyl acetate (20 ml). The aqueous solution was extracted with ethyl acetate (2x20 ml) and the combined organic solutions were washed with brine, dried over sodium sulphate and evaporated under reduced pressure. The residual orange oil was purified by chromatography on silica gel using methanol in dichloromethane as eluant (gradient from 0:100 to 4:96) to give the title compound (16 mg).

^{1}H NMR (400MHz, $CDCl_3$): δ 1.88 (d, 2H), 2.16 (m, 2H), 2.34 (s, 3H), 3.76 (d, 2H), 5.09 (s, 2H), 6.84 (m, 1H), 6.93 (d, 2H), 6.98 (d, 2H), 7.24 (m, 2H), 7.38 (m, 3H).

LCMS: *m/z* ES^+ 333 $[M+H]^+$

Example 23: 2-[4-(4-Benzyl-5-methyl-4*H*-[1,2,4]triazol-3-yl)-piperidin-1-yl]-pyrazine



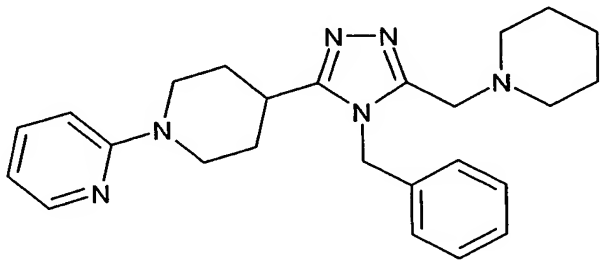
The piperidine of Preparation 29 (164 mg, 0.5 mmol) was mixed with 2-chloropyrazine (143 mg, 1.25 mmol) and diisopropylethylamine (129 µl, 1 mmol) in 1,4-dioxane (10 ml) and was heated under reflux for 3 hours. N,N-dimethylformamide (4 ml) was added and the mixture was heated at 100°C for 48 hours. The solvent was evaporated under reduced pressure and the residue was dissolved in ethyl acetate (20 ml). The organic solution was washed with water (20 ml) and brine (20 ml), dried over magnesium sulphate and evaporated under reduced pressure. The residue was purified by chromatography on silica gel using methanol in dichloromethane as eluant (0.7:99.3) to give the title compound as an off white solid (45 mg).

M.p. 191.1°C

^{1}H NMR (400MHz, $CDCl_3$): δ 1.83 (m, 2H), 2.01 (m, 2H), 2.83 (s, 3H), 2.90 (m, 1H), 2.96 (m, 2H), 4.82 (m, 2H), 5.07 (s, 2H), 6.94 (m, 2H), 7.84 (m, 3H), 7.80 (d, 1H), 8.01 (m, 1H), 8.11 (d, 1H).

LCMS: ES^+ *m/z* 357 $[M+Na]^+$

Example 24: 4-(4-Benzyl-5-piperidin-1-ylmethyl-4H-[1,2,4]triazol-3-yl)-3,4,5,6-tetrahydro-2H-[1,2']bipyridinyl



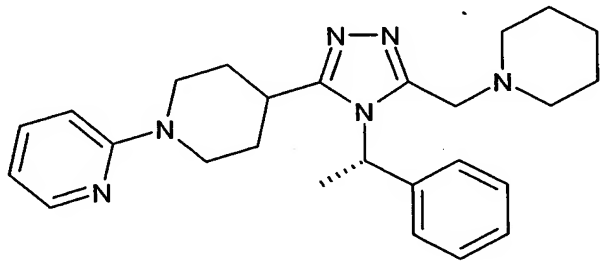
The oxadiazole of Preparation 40 (100 mg, 0.31 mmol), anhydrous magnesium chloride (10 mg, 0.11 mmol) and benzylamine (120 µl, 1.24 mmol) were heated at 150°C for 18

hours. The reaction mixture was cooled to room temperature and partitioned between dichloromethane and 2 N hydrochloric acid. The acidic solution was washed with dichloromethane (x2) and was basified by addition of solid sodium carbonate. The solid formed was isolated by filtration, washed with water and dried under vacuum to give the title compound as a white solid (100 mg).

^{1}H NMR (400MHz, CD_3OD): δ 1.48 (m, 6H), 1.73 (m, 2H), 1.87 (m, 2H), 2.39 (s, 4H), 2.82 (t, 2H), 2.99 (m, 1H), 3.58 (s, 2H), 4.29 (d, 2H), 5.48 (s, 2H), 6.62 (m, 1H), 6.81 (d, 1H), 7.16 (d, 2H), 7.38 (m, 3H), 7.53 (m, 1H), 8.03 (d, 1H)

LRMS: m/z APCI 377[M+H]$^+$

Example 25: (*S*)-4-[4-(1-Phenyl-ethyl)-5-piperidin-1-ylmethyl-4*H*-[1,2,4]triazol-3-yl]-3,4,5,6-tetrahydro-2*H*-[1,2']bipyridinyl

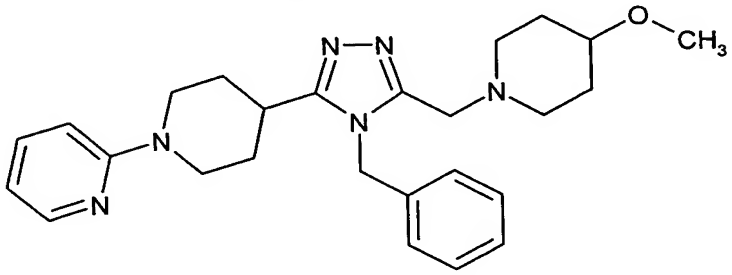


The title compound was obtained from the oxadiazole of Preparation 40 (115 mg, 0.35 mmol) and *S*-(-)-1-phenylethylamine in 33% yield following the procedure described in Example 24.

^{1}H NMR (400MHz, CD_3OD): (rotamers) δ 1.54 (m, 7H), 1.92 (m, 2H), 1.99 (d, 3H), 2.41 (m, 4H), 2.79 (m, 2H), 3.64 (dd, 2H), 4.05 (d, 2H), 4.33 (d, 2H), 6.08 (q, 1H), 6.62 (m, 1H), 6.79 (d, 1H), 7.40 (m, 5H), 7.51 (m, 1H), 8.01 (d, 1H)

LRMS: m/z APCI 377[M+H]$^+$

Example 26: 4-[4-Benzyl-5-(4-methoxy-piperidin-1-ylmethyl)-4*H*-[1,2,4]triazol-3-yl]-3,4,5,6-tetrahydro-2*H*-[1,2']bipyridinyl

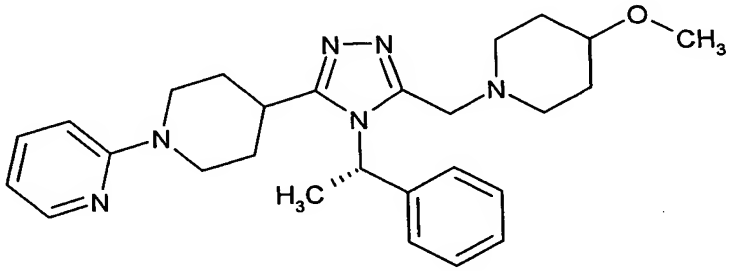


The title compound was obtained from the oxadiazole of Preparation 41 and benzylamine in 39% yield following the procedure described in Example 24.

^{1}H NMR (400MHz, CD_3OD): δ 1.41 (m, 2H), 1.74 (m, 2H), 1.85 (m, 4H), 2.21 (m, 2H), 2.68 (m, 2H), 2.83 (m, 2H), 2.99 (m, 1H), 3.30 (m, 4H), 3.60 (s, 2H), 4.28 (m, 2H), 5.49 (s, 2H), 6.62 (m, 1H), 6.81 (d, 1H), 7.15 (d, 2H), 7.38 (m, 3H)m 7.53 (m, 1H), 8.04 (m, 1H)

LRMS: m/z APCI 447$[M+H]^+$

Example 27: (*S*)-4-[5-(4-Methoxy-piperidin-1-ylmethyl)-4-(1-phenyl-ethyl)-4*H*-[1,2,4]triazol-3-yl]-3,4,5,6-tetrahydro-2*H*-[1,2']bipyridinyl

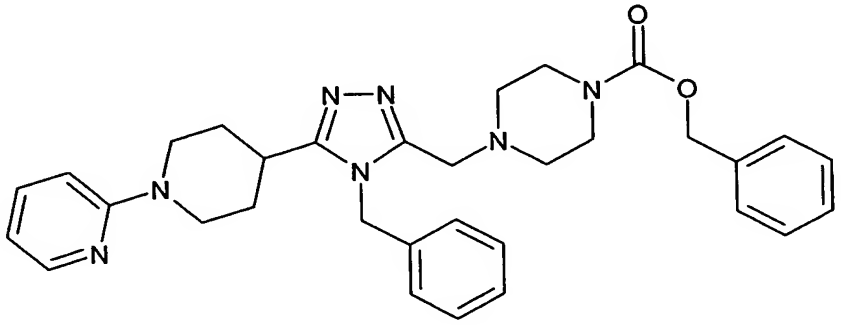


The title compound was obtained from the oxadiazole of Preparation 41 and *S*-(-)-1-phenylethylamine in 37% yield following the procedure described in Example 24.

^{1}H NMR (400MHz, CD_3OD): δ 0.90 (m, 1H), 1.55 (m, 3H), 1.93 (m, 4H), 1.99 (d, 3H), 2.26 (m, 2H), 2.40 (m, 1H), 2.79 (m, 4H), 3.33 (m, 4H), 3.68 (m, 2H), 4.06 (m, 1H), 4.35 (m, 1H), 6.08 (m, 1H), 6.61 (m, 1H), 6.79 (m, 1H), 7.43 (m 6H), 8.02 (m, 1H)

LRMS: m/z APCI 461 $[M+H]^+$

Example 28: 4-[4-Benzyl-5-(3,4,5,6-tetrahydro-2H-[1,2']bipyridinyl-4-yl)-4H-[1,2,4]triazol-3-ylmethyl]-piperazine-1-carboxylic acid benzyl ester

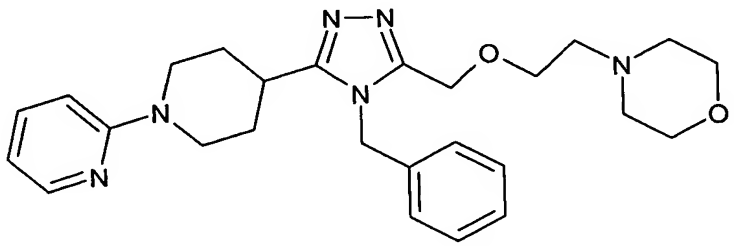


The oxadiazole of Preparation 42 (250 mg, 1.1 mmol), p-toluene sulphonic acid (20 mg) and benzylamine (176 µl, 3.3 mmol) were mixed in xylene (8 ml) and heated at 150°C for 18 hours. The solvent was evaporated under reduced pressure and the residue was partitioned between ethyl acetate (100 ml) and water (50 ml). The layers were separated and the organic layer was dried over magnesium sulphate and evaporated under reduced pressure. The residue was triturated with diethyl ether to give the title compound as a white solid (155 mg).

^{1}H NMR (400MHz, CD_3OD): δ 1.77 (m, 2H), 1.84 (m, 2H), 2.18 (s, 4 H), 2.82 (m, 2H), 3.01 (m, 1H), 3.33 (m, 4H), 3.63 (s, 2H), 4.28 (m, 2H), 5.09 (s, 2H), 5.74 (s, 2H), 6.62 (m, 1H), 6.81 (d, 1H), 7.11 (m, 2H), 7.30 (m, 8H), 7.52 (m, 1H), 8.02 (m, 1H)

LRMS: m/z APCI 461 $[M+H]^+$

Example 29: 4-[4-Benzyl-5-(2-morpholin-4-yl-ethoxymethyl)-4H-[1,2,4]triazol-3-yl]-3,4,5,6-tetrahydro-2H-[1,2']bipyridinyl



The title compound was obtained from the oxadiazole of Preparation 43 and benzylamine in 37% yield following the procedure described in Example 28.

^{1}H NMR (400MHz, CD_3OD): δ 1.70 (m, 2H), 1.83 (m, 2H), 2.41 (s, 4H), 2.47 (m, 2H), 2.81 (m, 2H), 2.97 (m, 1H), 3.59 (m, 4H), 3.62 (m, 2H), 4.27 (m, 2H), 4.65 (s, 2H), 5.43 (s, 2H), 6.62 (m, 1H), 6.81 (m, d, 1H), 7.16 (m, 2H), 7.38 (m, 3H), 7.53 (m, 1H), 8.04 (d, 1H)

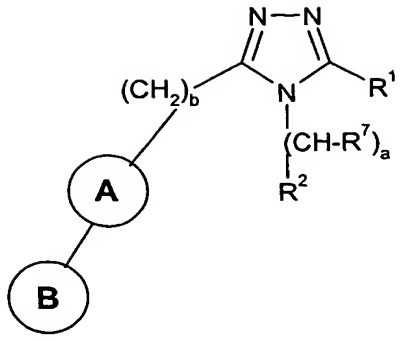
LRMS: m/z APCI 463 $[M+H]^+$

All of the compounds exemplified above showed a Ki value of less than 500 nM when tested in screen 1.0 (V_{1A} filter binding assay) as described above. Examples of specific compounds are illustrated in the table below

Example No.	Ki (nM)
4	8.6
16	13.19
17	4.67
24	12.08
25	16.12
26	4.5

CLAIMS:

1. A compound of formula **(I)**,



(I)

or a pharmaceutically acceptable salt or solvate thereof, wherein

R^1 represents C_1-C_6 alkyl, -$(CH_2)_c$-[C_3-C_8 cycloalkyl]-, -$(CH_2)_c$-W or -$(CH_2)_c$-Z-$(CH_2)_d$-W;

R^2 represents a phenyl group, optionally fused to a 5- or 6- membered aryl or heterocyclic group which may contain one or more heteroatoms selected from N, O or S; the phenyl group and the optionally fused group being optionally substituted with one or more groups independently selected from the list defined below;

Ring **A** represents a 4-, 5- or 6- membered saturated heterocyclic group containing at least one N;

Ring **B** represents a phenyl group or het^1, each group being optionally substituted with one or more groups independently selected from the list defined below;

het ^{1} represents a 4-, 5- or 6- membered saturated, or unsaturated, heterocyclic group containing at least one N (but which may also contain one or more O or S atoms);

R^7 independently represents H, C_1-C_6 alkyl, OR^3, -$(CH_2)_e$-R^3 or -$(CH_2)_f$-O-$(CH_2)_e$-R^3;

W represents a phenyl group, NR^4R^5 or het^2, the phenyl group being optionally substituted with one or more groups independently selected from halogen, CF_3, OCF_3, R^3, OR^3, CO_2R^3, $CONR^4R^5$, CN, $SO_2NR^4R^5$ and NR^3SO_2Me;

het^2 represents a 4-, 5-, 6- or 7- membered saturated, or unsaturated, heterocyclic group containing at least one N (but which may also contain one or more O or S atoms), optionally substituted with one or more groups independently selected from the list defined below;

Z represents O or $S(O)_g$;

g represents 0, 1 or 2;

het^3 represents a 4-, 5-, 6- or 7- membered saturated or unsaturated heterocyclic group containing at least one N (but which may also contain one or more O or S atoms), optionally substituted with one or more groups independently selected from the list defined below;

at each occurrence R^3 and R^6 independently represent H, C_1-C_6 alkyl optionally substituted by Y, $-(CH_2)_g$-[C_3-C_8 cycloalkyl], phenyl, benzyl, pyridyl or pyrimidyl;

Y independently represents a phenyl group, NR^4R^5 or het^3, the phenyl group being optionally substituted with one or more groups independently selected from halogen, CF_3, OCF_3, R^4, OR^4, CO_2R^4, $CONR^4R^5$, CN, $SO_2NR^4R^5$, NR^4SO_2Me and $-NR^4R^5$;

at each occurrence R^4 and R^5 independently represent H, C_1-C_6 alkyl, $-(CH_2)_g$-[C_3-C_8 cycloalkyl], phenyl, benzyl, pyridyl or pyrimidyl; or R^4 and R^5 together with the N atom to which they are attached represent a heterocyclic group of from 3 to 8 atoms;

substituents for R^2, Ring **B**, het^1, het^2 and het^3 are independently selected from the following list: halogen, CF_3, OCF_3, R^3, $-(CH_2)_e$-OR^3, $-(CH_2)_e$-CO_2R^3, $-(CH_2)_e$-$CONR^4R^5$, $-(CH_2)_e$-CN, $-(CH_2)_e$-$SO_2NR^4R^5$, $-(CH_2)_e$-NR^3SO_2Me, $-(CH_2)_e$-COR^3, $-(CH_2)_e$-$OCOR^3$, $-(CH_2)_e$-$NHCOR^3$, $-(CH_2)_e$-NR^3COR^6 and $-(CH_2)_eNR^4R^5$;

a and b independently represent 0 or 1;

c, d, e and g independently represent 0, 1, 2, 3 or 4;

f independently represents 1, 2, 3 or 4;

provided that a + b cannot equal 0; and

provided that when R^1 represents $-(CH_2)_c-Z-(CH_2)_d-W$ and W represents NR^4R^5 or any N linked heterocyclic group then d must not be 0 or 1; and

provided that when R^2 represents a phenyl group substituted by a group of formula $-(CH_2)_eOR^3$, $-(CH_2)_e-CO_2R^3$ or $-(CH_2)_eOCOR^3$; or
het^1 and/or het^2 are substituted by a group of formula $-(CH_2)_eOR^3$, $-(CH_2)_e-CO_2R^3$ or $-(CH_2)_eOCOR^3$; or
when R^7 represents $-OR^3$ or $-(CH_2)_f-O-(CH_2)_e-R^3$ and e is 0; or
when W represents a phenyl group substituted with $-OR^3$ or $-CO_2R^3$;
and R^3 represents an alkyl group substituted with Y, and Y represents NR^4R^5 or an N-linked het^3;
then R^3 must represent C_2-C_6 alkyl substituted with Y.

2. A compound according to claim 1, wherein R^2 is a phenyl group optionally substituted with one or more groups selected from halogen or $-(CH_2)_e-OR^3$.

3. A compound according to claim 1 or claim 2, wherein ring A is selected from piperidindiyl, piperazindiyl, azetidindiyl or pyrrolidindiyl.

4. A compound according to claim 3, wherein ring A is piperidindiyl.

5. A compound according to any of the preceding claims, wherein Z is O.

6. A compound according to any of the preceding claims, wherein het^1 is selected from optionally substituted pyridinyl, pyrimidinyl, pyrazinyl, pyridazinyl, triazinyl, triazolyl, tetrazolyl, pyrrolyl, pyrazolyl, imidazolyl, oxazolyl, isoxazolyl, thiazolyl, piperidinyl, piperazinyl, azetidinyl, morpholinyl, 2-oxa-5-aza-bicyclo[2.2.1.]heptanyl or pyrrolidinyl.

7. A compound according to any claim 6, wherein het^1 is selected from pyridinyl or pyrimidinyl, optionally by R^3.

8. A compound according to any of the preceding claims, wherein het^2 is selected from substituted or unsubstituted pyridinyl, pyrimidinyl, pyrazinyl, pyridazinyl, triazinyl, triazolyl, tetrazolyl, pyrrolyl, pyrazolyl, imidazolyl, oxazolyl, isoxazolyl, thiazolyl, piperidinyl,

piperazinyl, N-methyl piperazinyl, azetidinyl, morpholinyl, 2-oxa-5-aza-bicyclo[2.2.1]heptanyl or pyrrolidinyl.

9. A compound according to claim 8, wherein het^2 is selected from imidazolyl, piperidinyl, piperazinyl, N-methyl piperazinyl, azetidinyl, morpholinyl, 2-oxa-5-aza-bicyclo[2.2.1]heptanyl or pyrrolidinyl.

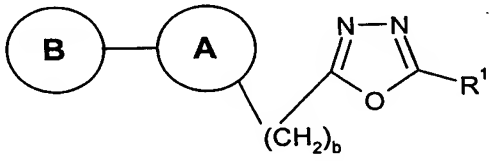
10. A compound according to any of the preceding claims, wherein a is 1 and b is 0.

11. A compound according to claim 1, which is selected from
(*S*)-4-[5-Butyl-4-(1-phenyl-ethyl)-4*H*-[1,2,4]triazol-3-yl]-3,4,5,6-tetrahydro-2*H*-[1,2']bipyridinyl;
2-[4-(4-Benzyl-5-isobutyl-4*H*-[1,2,4]triazol-3-yl)-piperidin-1-yl]-pyrimidine;
(*S*)-4-[5-Methyl-4-(1-phenyl-ethyl)-4*H*-[1,2,4]triazol-3-yl]-3,4,5,6-tetrahydro-2*H*-[1,2']bipyridinyl;
4-[4-Benzyl-5-butyl-4*H*-[1,2,4]triazol-3-yl]-3,4,5,6-tetrahydro-2*H*-[1,2']bipyridinyl;
2-[4-(4-Benzyl-5-isopropyl-4*H*-[1,2,4]triazol-3-yl)-piperidin-1-yl]-pyrimidine;
2-[4-(4-Benzyl-5-cyclopropyl-4*H*-[1,2,4]triazol-3-yl)-piperidin-1-yl]-pyrimidine;
(*S*)-2-{4-[5-Methyl-4-(1-phenyl-propyl)-4*H*-[1,2,4]triazol-3-yl)-piperidin-1-yl]-pyrimidine;
2-[4-(4-Benzyl-5-propyl-4*H*-[1,2,4]triazol-3-yl)-piperidin-1-yl]-pyrimidine;
2-{4-[4-Benzyl-5-(2-chloro-phenoxymethyl)-4*H*-[1,2,4]triazol-3-yl]-piperidin-1-yl}-pyrimidine;
2-[4-(4-Benzyl-5-butyl-4*H*-[1,2,4]triazol-3-yl)-piperidin-1-yl]-pyrimidine;
(*S*)-2-{4-[5-Methyl-4-(1-phenyl-ethyl)-4*H*-[1,2,4]triazol-3-yl)-piperidin-1-yl]-pyrimidine;
2-{4-[4-Benzyl-5-(4-fluoro-phenoxymethyl)-4*H*-[1,2,4]triazol-3-yl]-piperidin-1-yl}-pyrimidine;
2-{4-[5-Methyl-4-(3-methyl-benzyl)-4*H*-[1,2,4]triazol-3-yl)-piperidin-1-yl]-pyrimidine;
(*S*)-2-{4-[5-Methyl-4-(1-phenyl-ethyl)-4*H*-[1,2,4]triazol-3-ylmethyl]-piperidin-1-yl}-pyrimidine;
2-{4-[4-(3-Fluoro-benzyl)-5-methyl-4*H*-[1,2,4]triazol-3-yl)-piperidin-1-yl]-pyrimidine;
4-(4-Benzyl-5-morpholin-4-ylmethyl-4*H*-[1,2,4]triazol-3-yl)-3,4,5,6-tetrahydro-2*H*-[1,2']bipyridinyl;
4-(4-Benzyl-5-benzyloxymethyl-4*H*-[1,2,4]triazol-3-yl)-3,4,5,6-tetrahydro-2*H*-[1,2']bipyridinyl;
4-(4-Benzyl-5-methyl-4*H*-[1,2,4]triazol-3-yl)-3,4,5,6-tetrahydro-2*H*-[1,2']bipyridinyl;
(*R*)-2-[3-Methyl-5-(1-pyrimidin-2-yl-piperidin-4-yl)-[1,2,4]triazol-4-yl]-2-phenyl-ethanol;
2-[4-(4-Benzyl-5-methyl-4*H*-[1,2,4]triazol-3-yl)-piperidin-1-yl]-4-methyl-pyrimidine;

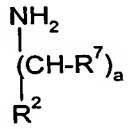
2-[4-(4-Benzyl-5-methyl-4*H*-[1,2,4]triazol-3-yl)-piperidin-1-yl]-pyrimidine;
4-(4-Benzyl-5-methyl-4*H*-[1,2,4]triazol-3-yl)-1-phenyl-piperidine;
2-[4-(4-Benzyl-5-methyl-4*H*-[1,2,4]triazol-3-yl)-piperidin-1-yl]-pyrazine;
4-(4-Benzyl-5-piperidin-1-ylmethyl-4H-[1,2,4]triazol-3-yl)-3,4,5,6-tetrahydro-2H-[1,2']bipyridinyl;
(*S*)-4-[4-(1-Phenyl-ethyl)-5-piperidin-1-ylmethyl-4*H*-[1,2,4]triazol-3-yl]-3,4,5,6-tetrahydro-2*H*-[1,2']bipyridinyl;
4-[4-Benzyl-5-(4-methoxy-piperidin-1-ylmethyl)-4*H*-[1,2,4]triazol-3-yl]-3,4,5,6-tetrahydro-2*H*-[1,2']bipyridinyl;
(*S*)-4-[5-(4-Methoxy-piperidin-1-ylmethyl)-4-(1-phenyl-ethyl)-4*H*-[1,2,4]triazol-3-yl]-3,4,5,6-tetrahydro-2*H*-[1,2']bipyridinyl;
4-[4-Benzyl-5-(3,4,5,6-tetrahydro-2H-[1,2']bipyridinyl-4-yl)-4H-[1,2,4]triazol-3-ylmethyl]-piperazine-1-carboxylic acid benzyl ester;
4-[4-Benzyl-5-(2-morpholin-4-yl-ethoxymethyl)-4H-[1,2,4]triazol-3-yl]-3,4,5,6-tetrahydro-2H-[1,2']bipyridinyl..

12. A process for the production of a compound of formula **(I)**, which comprises:

a) reacting a compound of formula **(II)** with a compound of formula **(III)**



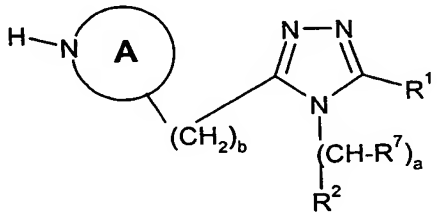
(II)



(III)

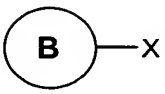
in which ring A and ring B, R^1, R^2, R^{42}, a and b are as defined in claim 1.

b) reacting a compound of formula **(VI)**



(VI)

in which ring A, R^1, R^2, R^{42}, a and b are as hereinbefore defined, with a compound of formula **(VII)**



(VII)

in which ring B is as defined above and X represents a leaving group such as halogen.

13. The use of a compound according to formula **(I)** as a medicament.

14. A method of treatment of aggression, Alzheimer's disease, anorexia nervosa, anxiety disorder, asthma, atherosclerosis, cardiac failure, cardiovascular disease, cataract, central nervous system disease, cerebrovascular ischemia, cirrhosis, cognitive disorder, Cushing's disease, depression, diabetes mellitus, dysmenorrhoea, edema, emesis, endometriosis, gastrointestinal disease, glaucoma, gynaecological disease, heart disease, hypertension, hyponatremia, ischemia, ischemic heart disease, lung tumor, micturition disorder, motion sickness, neoplasm, nephrotoxicity, non-insulin dependent diabetes, obesity, obsessive/compulsive disorder, ocular hypertension, premature labor, pulmonary disease, Raynaud's disease, renal disease, renal failure, male and female sexual dysfunction, sleep disorder, spinal cord injury, thrombosis, urogenital tract infection, urolithiasis, comprising administering a therapeutically effective amount of a compound of formula **(I)** to a patient suffering from such a disorder.

15. A method according to claim 15, wherein the disorder is dysmenorrhoea.

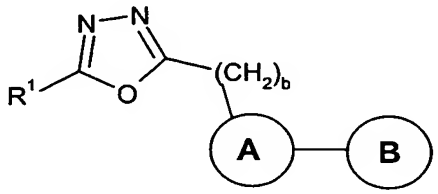
16. The use of a compound of formula **(I)** in the manufacture of a medicament for the treatment of aggression, Alzheimer's disease, anorexia nervosa, anxiety disorder, asthma, atherosclerosis, cardiac failure, cardiovascular disease, cataract, central nervous system disease, cerebrovascular ischemia, cirrhosis, cognitive disorder, Cushing's disease, depression, diabetes mellitus, dysmenorrhoea, edema, emesis, endometriosis, gastrointestinal disease, glaucoma, gynaecological disease, heart disease, hypertension, hyponatremia, ischemia, ischemic heart disease, lung tumor, micturition disorder, motion sickness, neoplasm, nephrotoxicity, non-insulin dependent diabetes, obesity, obsessive/compulsive disorder, ocular hypertension, premature labor, pulmonary disease,

Raynaud's disease, renal disease, renal failure, male and female sexual dysfunction, sleep disorder, spinal cord injury, thrombosis, urogenital tract infection, urolithiasis.

17. Use according to claim 16, for the treatment of dysmenorrhoea.

18. A pharmaceutical formulation including a compound of formula **(I)** or a pharmaceutically acceptable salt or solvate thereof, together with a pharmaceutically acceptable excipients, diluent or carrier;

19. An intermediate of formula **(II)**:



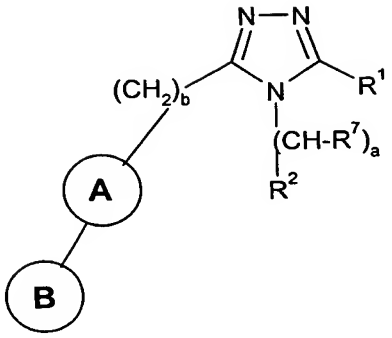
(II)

wherein R^1, rings A and B, and b are as defined in claim 1.

ABSTRACT:

Triazole Compounds Useful in Therapy

A compound of formula **(I)**,



(I)

or a pharmaceutically acceptable salt or solvate thereof, wherein

R^1 represents C_1-C_6 alkyl, -$(CH_2)_c$-[C_3-C_8 cycloalkyl]-, -$(CH_2)_c$-W or -$(CH_2)_c$-Z-$(CH_2)_d$-W;

R^2 represents a phenyl group, optionally fused to a 5- or 6- membered aryl or heterocyclic group which may contain one or more heteroatoms selected from N, O or S; the phenyl group and the optionally fused group being optionally substituted.;

Ring **A** represents a 4-, 5- or 6- membered saturated heterocyclic group containing at least one N;

Ring **B** represents a phenyl group or het^1, each group being optionally substituted;

het^1 represents a 4-, 5- or 6- membered saturated, or unsaturated, heterocyclic group containing at least one N (but which may also contain one or more O or S atoms);

R^7 independently represents H, C_1-C_6 alkyl, OR^3, -$(CH_2)_e$-R^3 or -$(CH_2)_f$-O-$(CH_2)_e$-R^3;

W represents a phenyl group, NR^4R^5 or het^2, the phenyl group being optionally substituted;

het^2 represents an optionally substituted 4-, 5-, 6- or 7- membered saturated, or unsaturated, heterocyclic group containing at least one N (but which may also contain one or more O or S atoms);

Z represents O or $S(O)_g$;

g represents 0, 1 or 2;

het^3 represents an optionally substituted 4-, 5-, 6- or 7- membered saturated or unsaturated heterocyclic group containing at least one N (but which may also contain one or more O or S atoms);

At each occurrence R^4 and R^5 independently represent H, C_1-C_6 alkyl, -$(CH_2)_g$-[C_3-C_8 cycloalkyl], phenyl, benzyl, pyridyl or pyrimidyl; or R^4 and R^5 together with the N atom to which they are attached represent a heterocyclic group of from 3 to 8 atoms;

a and b independently represent 0 or 1;

c, d, e and g independently represent 0, 1, 2, 3 or 4;

f independently represents 1, 2, 3 or 4;

provided that a + b cannot equal 0; and

provided that when R^1 represents -$(CH_2)_c$-Z-$(CH_2)_d$-W and W represents NR^4R^5 or any N linked heterocyclic group then d must not be 0 or 1; and

provided that when R^2 represents a phenyl group substituted by a group of formula -$(CH_2)_eOR^3$, -$(CH_2)_e$-CO_2R^3 or -$(CH_2)_eOCOR^3$; or

het^1 and/or het^2 are substituted by a group of formula -$(CH_2)_eOR^3$, -$(CH_2)_e$-CO_2R^3 or -$(CH_2)_eOCOR^3$; or

when R^7 represents -OR^3 or -$(CH_2)_f$-O-$(CH_2)_e$-R^3 and e is 0; or

when W represents a phenyl group substituted with -OR^3 or -CO_2R^3;

and R^3 represents an alkyl group substituted with Y, and Y represents NR^4R^5 or an N-linked het^3;

then R^3 must represent C_2-C_6 alkyl substituted with Y.

at each occurrence R^3 and R^6 independently represent H, C_1-C_6 alkyl optionally substituted by Y, -$(CH_2)_g$-[C_3-C_8 cycloalkyl], phenyl, benzyl, pyridyl or pyrimidyl;

Y independently represents a phenyl group, NR^4R^5 or het^3, the phenyl group being optionally substituted;

At each occurrence R^4 and R^5 independently represent H, C_1-C_6 alkyl, -$(CH_2)_g$-[C_3-C_8 cycloalkyl], phenyl, benzyl, pyridyl or pyrimidyl; or R^4 and R^5 together with the N atom to which they are attached represent a heterocyclic group of from 3 to 8 atoms;

a and b independently represent 0 or 1;

c, d, e and g independently represent 0, 1, 2, 3 or 4;

f independently represents 1, 2, 3 or 4;

provided that a + b cannot equal 0; and

provided that when R^1 represents -$(CH_2)_c$-Z-$(CH_2)_d$-W and W represents NR^4R^5 or any N linked heterocyclic group then d must not be 0 or 1; and

provided that when R^2 represents a phenyl group substituted by a group of formula -$(CH_2)_eOR^3$, -$(CH_2)_e$-CO_2R^3 or -$(CH_2)_eOCOR^3$; or

het^1 and/or het^2 are substituted by a group of formula -$(CH_2)_eOR^3$, -$(CH_2)_e$-CO_2R^3 or -$(CH_2)_eOCOR^3$; or

when R^7 represents -OR^3 or -$(CH_2)_f$-O-$(CH_2)_e$-R^3 and e is 0; or

when W represents a phenyl group substituted with $-OR^3$ or $-CO_2R^3$;
and R^3 represents an alkyl group substituted with Y, and Y represents NR^4R^5 or an N-linked het^3;
then R^3 must represent C_2-C_6 alkyl substituted with Y.